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## Original Communications

# THE EFFECT OF A LOW FAT DIET ON THE SPONTANEOUSLY OCCURRING ARTERIOSCLEROSIS OF THE CHICKEN

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THERE has long been a belief that dietary factors, particularly fats and cholesterol, may play an important role in the pathogenesis of atherosclerosis. Aschoff, on the basis of his studies on human and animal material, was of the opinion that some degree of lipemia was always necessary if atherosclerosis were to appear. He said, "From plasma of low cholesterol content no deposition of lipoids will occur even though the mechanical conditions are favorable."[1] The view that hypercholesterolemia and hyperlipemia are essential for the development of atherosclerosis was fortified considerably by the experimental production of atherosclerosis in numerous animal species by cholesterol feeding.[2,3,4] It has also received added support from clinical correlations of the diet and the incidence of atherosclerosis among different ethnic groups in widely different areas of the world. Rosenthal[5] and Hueper,[6] who have reviewed this subject, concluded that wherever and whenever fat constituted a large proportion of the diet, marked arteriosclerosis was prevalent. Wilens[7] has noted a correlation between the state of nutrition and the incidence and severity of atherosclerosis. Thus, overnutrition is associated with a higher incidence of atherosclerosis than is undernutrition.

Observation on the treatment of diabetics in recent years, with a low calorie, low fat, high carbohydrate diet, tends to indicate that with this regime the incidence of arteriosclerosis has declined, as compared with the incidence under

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the high fat diets previously employed.[9] In his recent survey of this aspect of diabetes, Root stated, "We believe that the chief cause of premature development of arteriosclerosis in diabetics, save for advancing age, is an excess of fat in the body (obesity), in the diet, and in the blood, due to lack of control of the diabetes."[10]

Recently Moreton[11] has advanced the theory that atherosclerosis is the result of the ingestion of many fatty meals over the course of a lifetime. On the basis of the foregoing suggestive evidence, some clinicians have been advocating the use of a low fat, low cholesterol diet in patients with atherosclerosis.

There is, however, no clear-cut clinical evidence that the data outlined are anything but suggestive. The difficulty has been in setting up adequately controlled experiments in man or in animals. The work of Fox[12] and of Dauber[13] has provided us with an experimental animal in which this problem may perhaps be elucidated. The chicken, in common with other members of the class *Aves*, develops atherosclerosis of the elastic and muscular arteries at a fairly early chronological age. By the age of one and one-half years more than 50 per cent of chickens show arterial lesions which resemble human atherosclerosis in many respects. In this preliminary experiment we have attempted to evaluate the effect of removing fat and cholesterol from the diet on the development of the spontaneous vascular changes in the chicken.

## METHODS

White leghorn cockerels approximately 6 to 10 weeks of age at the commencement of the experiment were divided into two groups. Group 1 consisted of sixteen chickens which received a diet of chick starter mash and water freely. Group 2 consisted of fourteen chickens which received a diet containing the same chick starter mash from which the cholesterol and fat had been removed by repeated alcohol ether extractions.* The diets were made approximately isocaloric by the addition of sucrose, and vitamins removed in the extraction procedure were replaced. Vitamins A, D, and E† were given in highly concentrated form in a few drops of cottonseed oil, and vitamin B was given in the form of bakers' yeast. The exact composition of the diets is detailed in Table I. The diet of Group 2 was a low fat diet containing essentially no cholesterol and approximately 0.1 to 0.3 per cent of fat, as compared with 3.0 to 5.0 per cent of fat in the control diet. It has been shown previously that chickens will remain healthy and grow on this fat extracted diet.[14]

Animals died or were sacrificed at intervals up to sixty-three weeks of feeding. The hearts and aortas were dissected out en bloc and carefully examined for evidence of atherosclerosis. Lesions, if any, were recorded on special forms and graded grossly 0 to 4 according to criteria previously described.[8] Sections were taken for microscopic examination from the aortas of all the birds. The chickens were bled from the alar vein at three- to four-week intervals and the total blood cholesterol was determined by the method of Schoenheimer and

*We are grateful to Armour Laboratories for extracting large quantities of mash.
†We are grateful to Lederle, Inc., for our vitamin supply.

TABLE I. COMPOSITION OF DIETS

| *Chick Starter Mash* | | *Fat Extracted Chick Starter Mash* | |
|---|---|---|---|
| Crude protein | 18.0% | Crude protein | 18.0% |
| Crude fat | 3–5% | Crude fat | 0.1–0.3% |
| Carbohydrate | 54% | Carbohydrate | 54% |
| Cholesterol | 0.06% | Sucrose* | 5% |
| | | Cholesterol | 0.0% |
| *Vitamin* | | *Vitamin* | |
| A | 1,800 USP per lb. | A | 1,200 USP per lb. |
| $D_3$ | 360 AOAC units per lb. | $D_3$ | 180 AOAC units per lb. |
| | | E | 30 mg. per lb. |
| | | B (brewers' yeast) | 9.08 Gm. per lb. |

*Ingredients*
Ground corn, ground oats, ground wheat, wheat bran, wheat middlings, alfalfa meal, meat and bone scraps, dried buttermilk, soy bean oil meal, steamed bone meal, calcium carbonate from limestone, salt 1.0 per cent, manganese sulfate 0.025 per cent, and potassium iodide, a trace.

*Added to mash.

Sperry.[15] Prior to the conclusion of the experiment at sixty-three weeks, 20 c.c. of blood was withdrawn under oil and a complete lipid analysis was done. The animals were sacrificed with Nembutal and the carcasses were defeathered and disemboweled. The intestines were opened and washed free of their contents. The livers were dissected free. The carcasses and viscera (except the liver), considered together as "carcass" in subsequent procedures, and the livers, were weighed wet, and then the carcasses were ground in an electric meat grinder until homogeneous mixtures were produced. The livers were minced and homogeneous samples taken. Blood and tissue lipids were determined on aliquots of alcohol-ether extract prepared according to the method of Man and Gildea[16] for blood, modified after Bloor[17] for tissues. For total fat, the aliquots of alcohol-ether extract were evaporated to dryness on a constant temperature, low-heat hot plate, and the lipid residue was re-extracted with petroleum ether, transferred quantitatively with repeated washings to tared beakers, evaporated to dryness, cooled to room temperature in a desiccator, and weighed. Fatty acids were determined on aliquots of alcohol-ether extract according to the method of Man and Gildea.[16] Blood lipid phosphorus was determined on aliquots of the alcohol-ether extract according to the Man and Peters[18] modification of the method of Fiske and Subbarow.[19] Total and free cholesterol were determined according to the method of Schoenheimer and Sperry[15] on alcohol-acetone extracts of blood and tissues prepared similarly to the alcohol-ether extracts. All determinations were carried out in duplicate.

## RESULTS

*Vascular Lesions.*—In Table III we have arranged the data to allow comparison between the two groups on the basis of duration of the feeding periods. It is evident that up to twenty-five weeks of feeding, none of the chickens on the low fat diet developed gross lesions of the aorta, while three out of five of the control chickens did. Between twenty-five and fifty weeks, two out of five of the

low fat group developed lesions, while five out of seven of the control group were similarly affected. Between fifty and sixty-three weeks, three out of four of the low fat chickens, and two out of four of the control group developed lesions of the aorta. Therefore, when the element of time is considered it appears that lesions developed sooner in the control birds than in birds fed a low fat diet. However, with prolongation of the feeding period beyond fifty weeks, the incidence in both groups became roughly the same. Taking the groups as a whole, gross lesions were seen in five of fourteen chickens on the low fat diet (35 per cent) and in ten of the sixteen chickens on the control diet (63 per cent). Table II illustrates clearly that the severity of the lesions was considerably greater in the control group than in the low fat group. It also indicates that whereas there was a difference in the incidence of gross lesions between the two groups, the incidence of microscopic lesions was about the same in both groups.

TABLE II. SUMMARY OF GROSS AND MICROSCOPIC GRADING OF LESIONS OF THE AORTA

| CONTROL GROUP | | | | | LOW FAT GROUP | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NO. | GROSS | | MICROSCOPIC | | NO. | GROSS | | MICROSCOPIC | |
| | THORAC. | ABD. | THORAC. | ABD. | | THORAC. | ABD. | THORAC. | ABD. |
| 154 | 0 | 0 | — | — | 86 | 0 | 0 | — | 0 |
| 92 | 0 | 0 | 0 | 0 | 72 | 0 | 0 | 0 | + |
| 157 | 0 | 1–2 | 0 | ++ | 71 | 0 | 0 | — | — |
| 96 | 0 | 1–2 | 0 | + | 74 | 0 | 0 | 0 | 0 |
| 91 | 0 | 1 | 0 | + | 84 | 0 | 0 | 0 | 0 |
| 99 | 0 | 0 | 0 | + | 75 | 0 | ¼-½ | 0 | ++ |
| 97 | 0 | 1 | 0 | + | 77 | 0 | 0 | 0 | + |
| 150 | 0 | 0 | 0 | — | 80 | ½ | 0 | 0 | + |
| 89 | 1–2 | 1 | + | 0 | 83 | 0 | 0 | 0 | + |
| 152 | 0 | 1 | 0 | + | 81 | 0 | 0 | 0 | ++ |
| 98 | 0 | 2 | 0 | +++ | | | | | |
| 100 | 0 | 1 | 0 | +++ | | | | | |
| 93 | 0 | 1 | 0 | ++ | 78 | 0 | 1 | 0 | +++ |
| 90 | 0 | 1–2 | 0 | ++ | 79 | 0 | 0 | 0 | 0 |
| 99 | 0 | 0 | 0 | + | 76 | ½ | 0 | 0 | 0 |
| 94 | 0 | 0 | 0 | + | 82 | ¼ | 0 | ++ | ++ |

In our cockerels the lesions were largely limited to the muscular aorta, which consisted of the descending thoracic and abdominal portions of the aorta. The abdominal aorta was by far the most common site of change. In most instances the intima of the abdominal aorta was elevated by a longitudinal white or yellow ridgelike thickening in the interrenal area (Fig. 1). The white ridgelike area occurred with equal frequency in both groups, but the incidence of grossly yellow lesions was much higher in the control group than in the low fat group. One bird in the control group showed thickening of the intima of the ascending portion of the thoracic aorta and distinct yellow nodular lesions of the brachiocephalic vessels. Two birds of the low fat group showed bright yellow unraised areas

in the arch of the aorta. A third showed a slightly raised, scaly white plaque in the arch of the aorta.

TABLE III. INCIDENCE OF GROSS LESIONS

| DURATION OF FEEDING PERIOD (WEEKS) | CONTROL GROUP | | | LOW FAT GROUP | | |
|---|---|---|---|---|---|---|
| | NO. OF CHICKENS | NO. WITH LESIONS | PER CENT WITH LESIONS | NO. OF CHICKENS | NO. WITH LESIONS | PER CENT WITH LESIONS |
| 0–25 | 5 | 3 | 60 | 5 | 0 | 0 |
| 26–50 | 7 | 5 | 71 | 5 | 2 | 40 |
| 51–63 | 4 | 2 | 50 | 4 | 3 | 75 |
| Total | 16 | 10 | 63 | 14 | 5 | 35 |

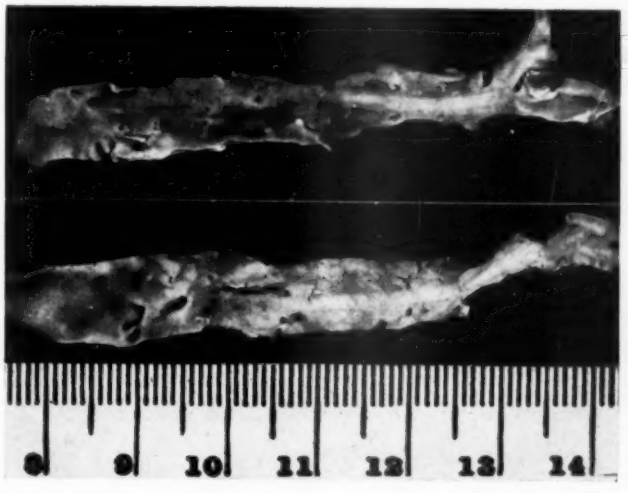


**Fig. 1.—Photograph of the muscular aorta of two chickens, that is, the descending portion of thoracic and abdominal aorta. Note prominent ridgelike elevation in interrenal area. This is the characteristic location of the "spontaneous" lesions.**

*Microscopic Pathology.**—In both groups the lesions of the muscular aorta, as seen in sections stained with hematoxylin-eosin, and in frozen sections stained with Sudan IV, were essentially similar and were identical with those previously described by Dauber and Katz.[3] The intima was thickened to a varying degree by fibrocellular connective tissue which was young and cellular in regions of little proliferation and also at the surface of large plaques. The deeper portions of the placques were composed of dense acellular connective tissue with areas of hyaline degeneration of the collagen and with fusiform cholesterol crystal clefts and calcific granules. In some cases the deeper layers of the fibrous plaques

***We are indebted to Dr. O. Saphir of the Department of Pathology for checking random specimens with us.**

contained large, pale foam cells. Fat stains showed varying quantities of lipids in the depths of the thickened intima and also in the adjacent tissue of the media. Figs. 2 and 3 illustrate the typical appearance of the spontaneous lesions stained with hematoxylin-eosin and in frozen section. These lesions are typical atheromas.

Fig. 2.

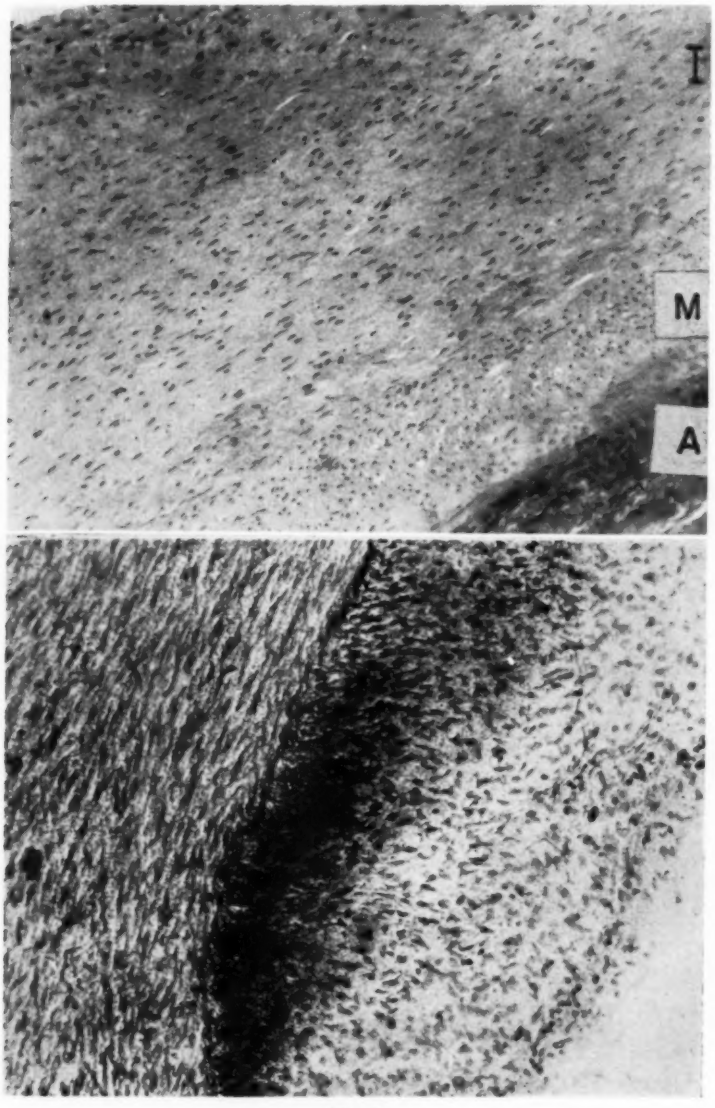


Fig. 3.

**Fig. 2.—Hematoxylin-eosin stained paraffin sections (× 160) from control bird fed ordinary mash for fifty-plus weeks. There is marked thickening of the intima (*I*) which is fibrocellular in nature. Depths of plaque show more collagen, and hyalinization of the connective tissue has occurred. Area next to media (*M*) shows mucoid degeneration and is the site of fat deposition. *A* is adventitia.**

**Fig. 3.—Frozen section (× 320) stained with Sudan IV from control bird fed ordinary mash for fifty-plus weeks. Note marked thickening of intima, largely cellular in nature. There is a heavy deposition of sudanophile material in the depths of the intima, adjacent to the media.**

One of the chickens from the low fat group (No. 78) showed marked involvement of the abdominal aorta on gross inspection. Microscopically there was typical intimal involvement with sudanophil material in the depths of the plaque along the intimal medial boundary and scattered heavily throughout the media. The entire vessel wall was infiltrated with mononuclear cells. This was not seen in any of the other birds.

The lesions of the elastic thoracic aorta differed from those of the abdominal aorta. Thus, in No. 82 of the low fat group, the lesion consisted almost entirely of medial involvement. There was deposition of large and small fat droplets in the ground substance of the media between essentially normal looking tissues and in areas of apparent degeneration of muscle tissue. There was negligible involvement of the intima.

Unfortunately, the series was too small to allow us to judge whether there was a quantitative difference in the amount of fat in the lesions of the control and low fat series.

It is concluded, therefore, that gross lesions were more frequent and severe in the control group than in the low fat group. Microscopically atheromatosis was present in both groups and the structure of the lesions was essentially similar.

*Blood and Tissue Lipid Determinations.*—The results are summarized in Table IV. The average live weights of the two groups at the conclusion of the experiment were almost identical, the low fat group averaging 1,848 grams and the control group 1,857 grams. Likewise, the group averages of liver weights were similar, being 19.6 grams for the low fat group and 22.9 grams for the control group. These data, plus the condition of the animals on inspection and

TABLE IV. LIPID ANALYSES: COMPOSITE CHART OF AVERAGE VALUES FOR TWO GROUPS OF CHICKENS

| | LIPID P (MG. %) | PHOSPHOLIPID (MG. %)* | TOTAL CHOLESTEROL (MG. %) | FREE CHOLESTEROL (MG. %) | CHOLESTEROL ESTERS (MG. %) | TOTAL FATTY ACIDS (MG. %)† |
|---|---|---|---|---|---|---|
| Blood Lipids: Control group | 6.02 | 156.5 | 98 | 27 | 71 | 196 |
| Blood Lipids: Low fat group | 6.71 | 174.4 | 125 | 43 | 82 | 243 |
| Liver Lipids: Control group | | | 307 | 272 | 35 | |
| Liver Lipids: Low fat group | | | 357 | 297 | 60 | |
| Carcass Lipids: Control group | | | 110 | 100 | 10 | |
| Carcass Lipids: Low fat group | | | 107 | 97 | 10 | |

*Expressed as lecithin: lipid P × 26.
†Expressed as palmitic acid.

the lack of pathological findings at necropsy, confirm that the low fat diet used was adequate nutritionally and permitted normal growth and development.

The blood lipid analyses reveal a suggestive, slight (10 to 20 per cent) elevation of each of the lipid fractions of the low fat group over those of the control group. It is to be noted that throughout the experiment the periodic routine blood cholesterol determinations revealed a consistent (10 to 20 per cent) increase in this constituent for the low fat group (Fig. 4).

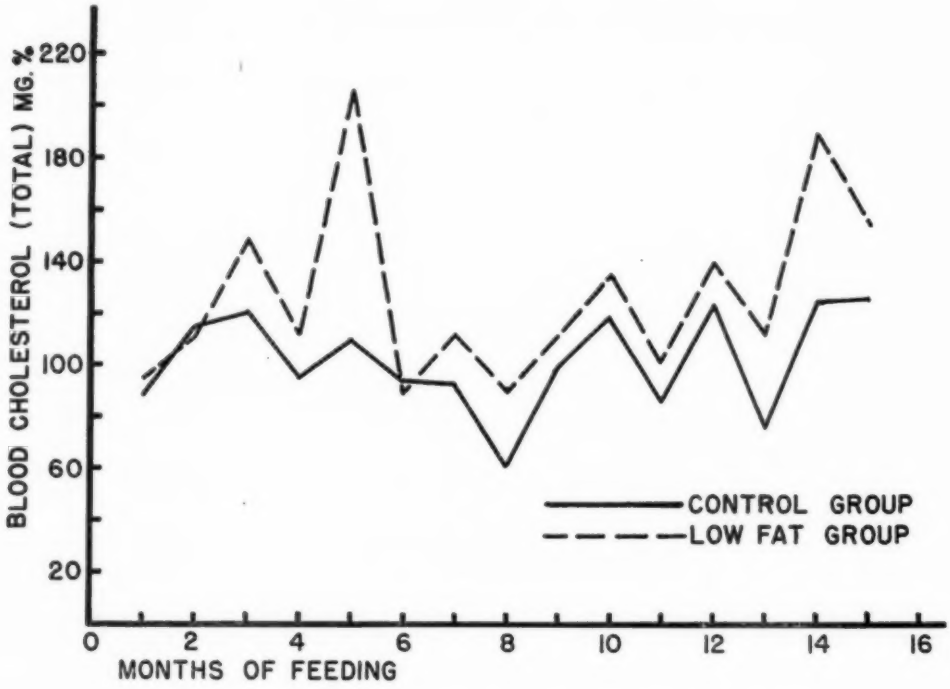


Fig. 4.—Average blood cholesterol levels of control and low fat group of chickens.

The liver cholesterols of the two groups were essentially similar, with certain small differences which are not significant statistically because of the small number of birds analyzed and the range of the values.

The lipid constituents of the carcass showed no significant variations between the two groups.

TABLE V. FECAL LIPID EXCRETION

| | TOTAL FAT (MG. %) | TOTAL FAT (24 HOURS) | FATTY ACIDS (MG. %) | FATTY ACIDS (24 HOURS) | LIPID P (MG. %) |
|---|---|---|---|---|---|
| Low fat group (4 chicks) | 500 | 1,490 mg. | 358 | 1,070 mg. | trace |
| Control group (4 chicks) | 595 | 1,465 mg. | 361 | 885 mg. | trace |

Studies of the fecal lipids revealed that with respect to the per cent of lipid in the feces and the total twenty-four hour lipid excretion, the two groups were remarkably similar (Table V).

Our data on chicken lipid analyses are similar to those reported in the literature by other workers.[20]

## DISCUSSION

Our results indicate that the restriction of fat and cholesterol in the diet of the chicken to very low levels does not prevent the development of spontaneous atherosclerosis in that species. There is, however, suggestive evidence that the severity of the lesions is less when fat is restricted. Thus, the number of gross yellow lesions was higher in the control group than in the low fat group, whereas the number of lesions visible under the microscope was about the same in both groups of birds.

The theoretical implication of this is twofold. First, it negates the necessity for invoking exogenous lipid and hyperlipemia in the pathogenesis of the naturally occurring lesions, and second, it indicates that although exogenous lipid is not essential to atherosclerogenesis it nevertheless tends to accelerate its progress and to increase its severity.

It would seem then that the so-called "endogenous lipid level" is adequate to permit the process of atherosclerogenesis to proceed. This is of great interest because it brings the experimental aspect of atherosclerosis into line with prevailing clinical impressions. Most instances of human atherosclerosis occur in the presence of normal lipid levels in the blood. Cholesterol feeding experiments have failed to supply fundamental clues to the nature of human atherosclerosis because they represent an abnormal and highly exaggerated condition which has no true parallel in human atherosclerosis, with the possible exception of xanthomatosis with hypercholesterolemia and some cases of diabetes. The theories of Anitschkow[2] and Aschoff,[1] of Leary,[21] and latterly of Moreton[11] all invoke a temporary or permanent lipemia or chylomicronemia as the precursor of the atherosclerosis. Certainly the evidence afforded by our experiments suggests that this view will have to be amended. We do not wish to deny the role of the lipids in arteriosclerosis. We merely wish to suggest that the "endogenous" or normal lipid concentration of the blood is adequate for the exercise of that role. When more lipid is made available, the influence of the lipids probably results in the acceleration and aggravation of the sclerotogenic process.

Our data on both blood and tissue lipids of chickens maintained for sixty-three weeks on a low fat diet indicate (1) that this species, in common with other laboratory animals, will thrive on a diet low in fat, and (2) that it is not possible to lower the level of the blood or tissue lipids by removing fat and cholesterol from the diet.

It is generally believed that the liver and the fat depots are the sites of synthesis of neutral fat and phospholipid from carbohydrate and protein residues in the diet.[22] Certainly it has been shown that cholesterol can be synthesized in the animal body from acetate residues derived from any source, and that the site of this synthesis is probably in the liver.[23] We also know that the synthesis of

fat from carbohydrate is a continuous process even when only small amounts of carbohydrate are fed.[24] The reserve ability of this conversion mechanism may be very great, as we have been able to demonstrate by implanting stilboestrol pellets into chickens on a low fat diet.[25] In such animals we were able to obtain massive lipemia and hypercholesterolemia and the development of atherosclerosis.

Our data on fecal lipid excretion indicate two things: (a) a remarkable constancy of excretion over a given period; (b) this constancy is independent of diet, at least for the conditions of this experiment. Chickens on a low fat diet for over sixty weeks continue to excrete the same amount of fecal lipid as do the control birds on regular mash. These findings are in full accord with previous reports.[26] They again confirm the fact that fecal lipids are not predominantly dietary fats which have escaped absorption, but rather are secretions of the intestinal mucosa.

There is no doubt that fat restriction will lower the blood cholesterol and lipids in patients with essential xanthomatosis of the hypercholesterolemic variety.[29] The blood lipids of normal persons, however, are strongly resistant to change by fat restriction and/or fat overfeeding.[30] As an inference from the animal experiments, it would seem that the evidence at present does not warrant wholesale restriction of lipids in attempt to prevent the onset of arteriosclerosis. There is suggestive evidence, however, that fat restriction may be a judicious measure in patients with hypercholesterolemia even of a moderate degree, and possibly in patients with a bad family history of coronary or cerebral arteriosclerosis. Certainly any wider application of fat restriction must await more experimental justification.

## SUMMARY

1. White leghorn cockerels, 6 to 10 weeks of age, were divided into two groups. Group 1 consisted of sixteen chickens which received in unlimited quantities a diet of chick starter mash and water. Group 2 consisted of fourteen chickens which received the same chick starter mash from which the fat and cholesterol had been largely removed by alcohol-ether extraction. This diet was made isocaloric by the addition of sucrose, and the vitamins removed in the extraction process were replaced. Feeding was continued for sixty-three weeks.

2. Gross atherosclerosis was seen in 35 per cent of the chickens on the low fat diet and in 63 per cent of the chickens on the control diet. The lesions appeared earlier and were more severe in the control group. The incidence of microscopically visible lesions was equal in both groups. There was no essential difference in the structure of the lesions.

3. The low fat group showed blood cholesterol levels which were consistently higher than those of the control group throughout the course of the experiment. Lipid analysis of the blood performed at the conclusion of the experiment revealed that all the lipid fractions of the blood were slightly higher in the low fat group than in the control group.

We are greatly indebted to the technical team whose efforts were essential for the proper execution of this study, and especially to Mrs. L. Havel and Miss C. Bolene, both Deborah V. Dauber Research Assistants, and to Miss Marilyn Dudley and Mrs. Eva Levinson, chemical technicians.

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# ANTICOAGULATION THERAPY WITH HEPARIN/PITKIN MENSTRUUM IN THE MANAGEMENT OF CORONARY ARTERY THROMBOSIS AND ITS COMPLICATIONS

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ANTICOAGULATION therapy with heparin/Pitkin menstruum in the management of thromboembolic disease has been the subject of intensive study and prolonged trial.[1-9] Our aggregate series, totalling more than 450 patients with thrombotic disorders, received as the primary therapeutic measure several thousand subcutaneous deposits of heparin/Pitkin menstruum. The basic information gleaned from the comprehensive experimental study and clinical experience with this anticoagulation preparation in venous thromboembolism was applied in the treatment of patients with various types of arterial thrombotic lesions, including coronary artery occlusion. The response to the treatment program in a clinically and electrocardiographically authentic series of patients with acute coronary artery thrombosis was sufficiently gratifying to justify this preliminary communication.

## CLINICAL MATERIAL

The twenty patients with coronary artery thrombosis comprising this series were all acutely, and many gravely, ill. This group of patients, the majority of whom had serious complications, were well suited for assessing the effects of anticoagulation therapy. The clinical features and electrocardiographic findings in all these patients were classical (Table I).

Ten (50 per cent) of the patients, five of whom had previous coronary artery closures, were referred three to seventy-two hours after onset during the early phases of the disease when optimum results from the treatment program might be expected. The ages of these patients, eight men and two women, varied from 35 to 64 years, the average age being 44 years. Three of this group developed anterior wall infarctions and seven had posterior wall lesions; five of the ten patients had thromboembolic complications.

The remaining ten patients (50 per cent), four of whom had had previous coronary attacks, were admitted for treatment six to fifty-six days after onset of the acute coronary occlusion. These patients, seven men and three women, were in a more advanced age group; their ages ranged from 47 to 76 years, the

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TABLE I. HEPARIN/PITKIN MENSTRUUM THERAPY IN TWENTY PATIENTS WITH ACUTE CORONARY ARTERY THROMBOSIS

| CASE NO. | AGE | SEX | SIGNIFICANT PAST HISTORY | ELECTROCARDIOGRAPHIC FINDINGS | COMPLICATIONS | DURATION OF SYMPTOMS BEFORE HEPARINIZATION | HEPARIN/PITKIN MENSTRUUM THERAPY | | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | NO. DAYS | NO. DEPOSITS | TOTAL HEPARIN (MG.) | |
| 1 J. B. | 45 | F | None | Posterior wall infarction | Postoperative thrombophlebitis | 3 hours | 8 | 4 | 1,200 | Classical symptoms coronary thrombosis 18 days after hysterectomy; uneventful recovery |
| 2 W. P. | 41 | M | None | Anterior wall infarction with possible posterior wall involvement | Acute psychosis | 4 hours | 19 | 7 | 2,800 | Ambulatory on 20th day; no post-therapy heparinization; venous thromboembolic disease 2 months after discharge |
| 3 L. Z. | 64 | M | Hypertensive cardiovascular disease; coronary artery thrombosis | Posterolateral wall infarction | | 4 hours | 18 | 9 | 3,350 | Uneventful recovery |
| 4 M. G. | 35 | M | None | Anterior wall infarction | | 9 hours | 26 | 9 | 2,350 | Unusually extensive coronary occlusion |
| 5 A. G. | 52 | M | None | Posterolateral wall infarction | | 12 hours | 13 | 6 | 2,150 | Delayed electrocardiographic manifestations |
| 6 L. N. | 60 | F | Hypertensive cardiovascular disease; effort syndrome; diabetes mellitus | Acute posterior wall infarction | Thrombophlebitis left lower extremity | 24 hours | 30 | 9 | 1,900 | Good recovery from initial acute and subsequent fresh posterior wall infarction; heparin hyperreactor |
| 7 B. F. | 60 | M | Coronary artery thrombosis; effort syndrome | Anterior wall infarction | | 24 hours | 19 | 8 | 2,950 | Uneventful recovery |
| 8 H. B. | 59 | M | Atherosclerotic cardiovascular disease; coronary artery thrombosis | Posterior wall infarction superimposed on old myocardial changes | Recurrent thrombophlebitis; repeated embolizations | 48 hours | 18 | 8 | 2,600 | Patient is a thrombophiliac; repeated pulmonary embolizations despite vein ligation and Dicumarol; satisfactory recovery with heparin |
| 9 J. M. | 42 | M | Hypertensive cardiovascular disease; coronary artery thrombosis | Posterior wall infarction | Repeated pulmonary embolization | 72 hours | 26 | 10 | 3,150 | Embolizations promptly arrested by therapy |
| 10 M. R. B. | 43 | M | Coronary artery thrombosis (two attacks) | Posterior wall infarction superimposed on left ventricular strain | Pulmonary embolization; pleural effusion | 72 hours | 32 | 9 | 1,900 | Patient is a thrombophiliac; three distinct episodes of venous thromboembolism despite vein ligation; heparin hyperreactor |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 11 | M. O. | 76 | M | Hypertensive cardiovascular disease; coronary artery occlusion | Posterior wall infarction | Pulmonary infarction; pulmonary edema | 6 days | 40 | 9 | 2,450 | Was in moribund state when treatment was inaugurated; satisfactory recovery |
| 12 | S. L. | 47 | M | Atherosclerotic cardiovascular disease; coronary artery occlusion | Posterior wall infarction | Venous thromboembolic disease; pulmonary embolization | 6 days | 25 | 9 | 3,200 | Made spectacular recovery despite thrombophlebitis and pulmonary embolization which complicated second attack of coronary thrombosis |
| 13 | P. B. | 52 | F | Hypertensive cardiovascular disease; coronary artery thrombosis (two attacks); effort syndrome | Acute posterior wall infarction, left ventricular strain | Cerebral embolus from mural thrombus; hemiplegia; venous thromboembolic disease, pulmonary embolization | 7 days | 35 | 11 | 3,200 | Excellent recovery from hemiplegia to such an extent that patient became ambulatory and speech returned practically to normal; patient is a thrombophiliac |
| 14 | J. G. | 64 | M | Atherosclerotic cardiovascular disease; coronary artery disease | Posterior wall infarction | Pulmonary embolization | 7 days | 24 | 8 | 2,500 | Satisfactory recovery |
| 15 | C. H. H. | 61 | M | None | Anterior wall infarction; auricular fibrillation | Cerebral embolization, pulmonary edema; thrombophlebitis left lower extremity, pulmonary embolization | 11 days | 5 | 3 | 1,200 | Therapy as started after patient was in coma and virtually moribund for 4 days |
| 16 | B. T. | 59 | M | Hypertensive cardiovascular disease | Anterior wall infarction, auricular fibrillation, auricular flutter | Venous thromboembolic disease, pulmonary embolization | 14 days | 24 | 9 | 2,850 | Anticoagulation therapy begun after onset of bilateral phlebothrombosis and pulmonary embolization; uneventful recovery |
| 17 | U. R. | 59 | M | Coronary artery thrombosis | Posterior wall infarction | | 14 days | 12 | 4 | 1,500 | Uneventful recovery |
| 18 | M. H. | 59 | M | None | Anteroapical infarction | Cerebral artery embolization from mural thrombus | 32 days | 14 | 6 | 2,200 | No further episodes of embolization once heparnization was inaugurated |
| 19 | V. M. | 50 | F | Coronary artery disease | Anterior wall infarction with some extracardiac changes | Splenic infarct; possible venous thromboembolic disease | 42 days | 24 | 10 | 2,900 | Transitory nausea following injections; uneventful recovery |
| 20 | E. S. | 58 | F | Hypertensive cardiovascular disease; effort syndrome; diabetes mellitus | Posterior wall infarction | Venous thromboembolic disease; repeated pulmonary embolization | 56 days | 21 | 7 | 2,250 | Repeated pulmonary embolization despite Dicumarol; prompt termination of thromboembolic episodes with heparin therapy |

average being 58 years. Four of this group sustained anterior wall infarctions and six had posterior wall lesions. The high incidence (90 per cent) of thromboembolic complications, which was primarily responsible for instituting anticoagulation therapy, may be ascribable in part to the fact that these ten patients were in a generally older age group.

The gravity and prognostic import of the clinical manifestations in this series is but superficially portrayed in the tabulation of data. The appearance of clinically detectable, complicating thromboembolic episodes in fourteen of the twenty patients (70 per cent), as against a reported expectancy of 13.9 per cent,[10] is a reflection of the degree of myocardial involvement and resultant circulatory embarrassment.

## TREATMENT PROGRAM

A detailed description of the heparin/Pitkin menstruum preparation, including the rationale, indications, contraindications, and the various formulas which are now available,* has been presented in previous publications.[1-5, 9-11] As pointed out in these reports, it is essential to use the preparations without vasoconstrictor drugs in the management of patients with intra-arterial clotting, particularly when dealing with coronary artery thrombosis. In these patients it is important to achieve prompt and maximum anticoagulation responses. Therefore, the initial dose of heparin in the Pitkin menstruum should be at least 400 mg., administered subcutaneously in the usual manner. About 90 per cent of subjects are normal reactors; the remaining 10 per cent are either hyporeactors or hyperreactors and require greater or lesser dosages, respectively. All coagulation time determinations are estimated by a modified Lee-White-Howell method.[12] For effective heparinization the blood coagulation time should be not less than three times the control value, that is, 30 to 45 minutes, as contrasted with a control coagulcgram of 9 to 15 minutes. Prolongation of coagulation time after each individual deposit appears within one to two hours and endures for forty-eight hours or longer as a result of the retarding influence of the Pitkin menstruum (Fig. 1). It is comforting to know that injection of larger doses to insure satisfactory heparinization does not invite the hazard of excessive doses of Dicumarol. In the patient with an intact cardiovascular apparatus there is little or no risk of hemorrhage, even following excessive amounts of heparin sufficient to elevate the coagulation time considerably beyond the requisite level.

After the pattern of response has been ascertained, the subsequent injections can be made more or less routine. Repetitive doses of 400 mg. are generally given every other day during the acute thrombotic phase in order to prevent propagation and to promote resolution of the thrombus. This schedule should be maintained for three to four implants to achieve a continuous and adequate heparin response. Thereafter, if justified by the anticoagulation effects, the individual dose may be given at longer intervals and the amount of the drug per dose reduced to 300 mg. or even 200 mg., as dictated by the specific case. Occasionally, in the initial phases, deposits may have to be given on successive days in order to obtain optimum and sustained heparinization. As in venous throm-

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boembolic disease, the span of treatment must be continued at least until the patient is permitted out of bed. Occasionally patients who are on heparin therapy may, following abrupt withdrawal of the drug, develop a diphasic phenomenon wherein the blood becomes hypercoagulable. This phenomenon is obviated by a gradual decrease of the heparin/Pitkin menstruum therapy.

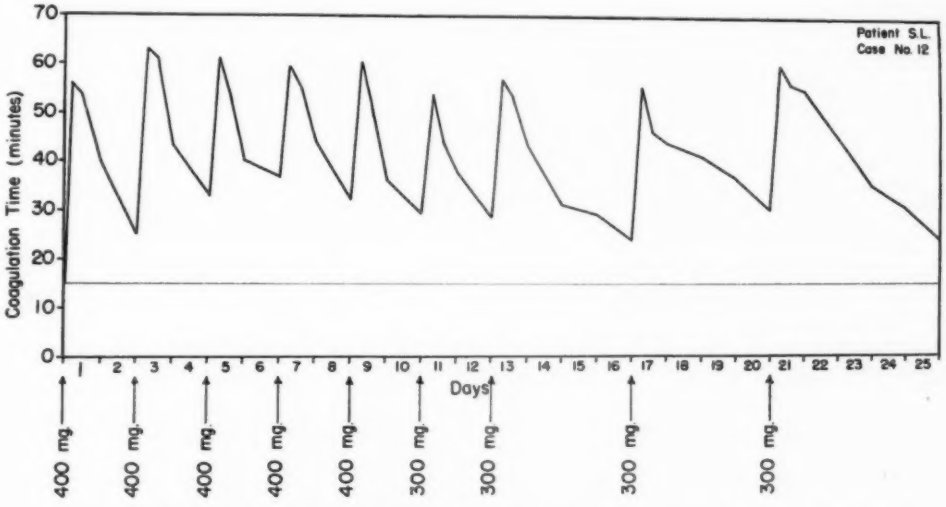


**Fig. 1.—Coagulogram of heparin/Pitkin menstruum treatment program in a normal reactor.**

The local pain, swelling, and tenderness of the earlier experimental, highly acid preparation was due to the precipitate which was found to be a combination of heparin and eucupine. The pain factor induced by the acidity and precipitate of the preparation was at times excessive but could be controlled by adequate sedation. This objection to the original preparation, the pain factor which was so disturbing to the patient, has now been controlled by careful buffering so that the pH of the gel is more acceptable physiologically and the tendency to precipitation noted in the original ampules has been overcome. Other side effects of the heparin/Pitkin menstruum preparation are trivial.[1-5, 7-9] On rare occasions some oozing will occur from the needle puncture. In the several thousand deposits that have been made there was but one instance of hematoma of sufficient proportion to justify interruption of heparinization; this patient with post-partum thrombophlebitis made an uneventful recovery.

Although we have not elicited any direct thromboplastic effect of digitalis, the drug has been reported to inhibit the anticoagulant action of heparin.[13,14] If possible, therefore, the use of digitalis is to be avoided during the period of heparinization. If suspension of heparin activity is desired, small transfusions of whole blood or relatively fresh bank blood will inactivate any circulating heparin. An ice bag to the site of deposit, or a tourniquet above it, will suspend or slow up the absorption of the drug. In our experience the use of protamine for immediate interruption of heparinization has not been necessary.

Adjuvant drug therapy is employed uniformly for sedation and to overcome vasospasm. For these purposes morphine sulfate, in adequate amounts, and Papaverine, in dosages of one and one-half to three grains intravenously or intramuscularly every four hours, remain the drugs of choice. These should be administered as promptly as possible after the onset of the characteristic pain. Ideally, the conjoint therapeutic attack at the very outset should be intravenous morphine, intramuscular Papaverine, and subcutaneous heparin in the Pitkin menstruum.

## RESULTS

The results in this exploratory study of twenty consecutive, unselected patients with acute coronary thrombosis are noted in Table I. Of the twenty patients, there was but one fatality (5 per cent); this patient (Case 15) had been desperately ill for eleven days and was moribund before anticoagulation therapy was inaugurated. This treatment failure occurred among the fourteen patients who exhibited thromboembolic complications. A brief review of Case 15 follows:

CASE 15.—C. H. H., a 61-year-old white man, a business executive, was admitted to the Lawrence Hospital, Bronxville, N. Y., under the care of Dr. H. E. McGarvey. The patient had a past history of "nervous stomach" since childhood. One day before admission he developed flatulence with increasing, constant, dull epigastric pain, dyspnea, and shock. His blood pressure was 100/72. On the midnight prior to admission the acute abdominal distress was of such severity that a surgical condition was suspected. A leucocytosis of 15,000 with 88 per cent polymorphonuclear leucocytes apparently pointed in the same direction. Two days later he developed a consolidation at the base of the right lung with a friction rub over the apical area of the heart; the heart sounds became less distinct and the clinical picture justified a diagnosis of coronary artery thrombosis. The following day the heart sounds were much poorer in quality. He developed cardiac embarrassment and mild shock, and his condition rapidly became critical. Successive electrocardiograms disclosed findings characteristic of an anterior myocardial infarction and auricular fibrillation. Seven days after onset the patient developed pulmonary edema and lapsed into a coma which was ascribed to extensive cerebral embolization from an intracardiac mural thrombus. On the eleventh day of his illness he exhibited right thrombophlebitis with massive pulmonary embolization. The congestive failure was advanced; he was comatose and practically moribund. Heparin/Pitkin menstruum was instituted at this juncture. Despite adequate anticoagulation responses, the patient rapidly deteriorated; he never regained consciousness and succumbed on the sixteenth day of his illness. He had, in all, five days of therapy with a total of 1,200 mg. of heparin in the Pitkin menstruum deposited in three injections

*Comment.*—This patient with anterior wall infarction and auricular fibrillation had cerebral embolization from an intracardiac mural thrombus and massive pulmonary embolization from peripheral vein thrombosis. When treatment was inaugurated the patient was in coma and desperately ill. Notwithstanding the gravity of the condition, anticoagulation therapy was started and proved unavailing after a five-day span of therapy.

All the remaining nineteen patients recovered despite previous coronary attacks and complicating thromboembolic episodes in a large percentage of the group. There are included the ten patients who were treated within three to seventy-two hours after onset of the acute coronary occlusion and the four patients whose prognosis was just as ominous as that in Case 15. Brief reviews of some illustrative cases in this group follow:

CASE 4.—M. G., a 35-year-old white physician, was referred for treatment* nine hours after the onset of his symptoms. This patient, who had never had any previous evidence of cardiovascular disease, was admitted to City Hospital, New York City, on May 2, 1947, with a history of sudden, excruciating, substernal, nonradiating pain of three hours' duration. On examination he was found to be very apprehensive and restless. He was in shock and slight cyanosis of the lips was present. The heart sounds were of only fair quality. The systolic blood pressure was 110, as compared with his normal of 130 millimeters of mercury. Temperature on admission was 98° F.; this rose to 103°F. on the following day and remained elevated for six days. The electrocardiogram on admission (Fig. 2) confirmed the diagnosis of acute myocardial infarction of the anterior wall type. Nine hours after the onset, anticoagulation therapy was instituted with 300 mg. of heparin in the Pitkin menstruum. The following day a similar dose was given because of the inadequate anticoagulation response. In all, the patient was given a total of 2,350 mg. of heparin/Pitkin menstruum deposited in nine injections over a period of twenty-six days. Periodic electrocardiograms taken during the course of the treatment disclosed progressive healing (Fig. 2), so much so that the patient was allowed out of bed after four weeks and was finally discharged after five and one-half weeks of hospitalization. There were no thromboembolic episodes or other untoward complications and there were no clinically evident residua.

*Comment.*—This patient was in critical condition when first seen following the unheralded attack of acute, severe myocardial infarction. Heparinization was initiated nine hours after onset. As a result of the prompt institution of anticoagulation therapy, the electrocardiograms, which on admission confirmed the presence of an acute anterior wall infarction, revealed progressive healing of the infarcted area so that the patient was able to get out of bed after twenty-six days of treatment and discharged from the hospital five and one-half weeks after admission. There was concurrent improvement in the clinical picture and there were no thromboembolic or other complications.

CASE 6.—L. N., a 60-year-old white housewife, was referred for treatment twenty-four hours after recurrent myocardial infarction. This patient, with a background of hypertensive, atherosclerotic cardiovascular disease and diabetes mellitus, had for six years typical angina of effort from which she obtained relief with nitroglycerine. Six weeks prior to her admission to the Beth Moses Hospital of Brooklyn, on March 15, 1947, the patient had a sudden attack of precordial pain with concomitant shock. A diagnosis of acute posterior wall infarction was made which was substantiated by electrocardiographic tracings. While getting out of bed, after six weeks of bed rest, the patient sustained an acute thrombophlebitis of the left leg with a rise in temperature. Twenty-four hours before admission there was a recurrence of severe precordial pain. On examination she exhibited shock, marked pallor, and distant heart sounds of very poor quality. There was also pain, tenderness, heat, and redness of the left calf. A diagnosis of coronary thrombosis and thrombophlebitis of the left lower extremity was made. A pretreatment electrocardiogram (Fig. 3) was interpreted as indicating an acute, posterior myocardial infarction with sinus tachycardia. Follow-up electrocardiograms taken during the course of treatment with heparin/Pitkin menstruum, which was begun promptly after admission, revealed progressive improvement (Fig. 3). The patient was a hyporeactor and required a total of 1,900 mg., given in nine injections over a period of thirty days. During this span of treatment the patient had no subjective complaints, the heart sounds improved, blood pressure gradually attained a higher level, and the thrombophlebitis of the left leg subsided completely.

*Comment.*—This patient, with thrombophilia and a background of hypertensive, atherosclerotic cardiovascular disease and diabetes mellitus, originally sustained an acute coronary closure with myocardial infarction which was treated in the usual manner with six weeks of bed rest. As a result of the venostasis, she developed an acute thrombophlebitis of the left lower extremity and in addition suffered an extension of the coronary artery thrombosis. With heparin/Pitkin menstruum therapy there was a reversion of the electrocardiogram toward normal within seven

*We wish to thank Dr. E. S. Bernecker, Commissioner, Department of Hospitals, New York City, for his interest and cooperation in referring clinical material for this study.

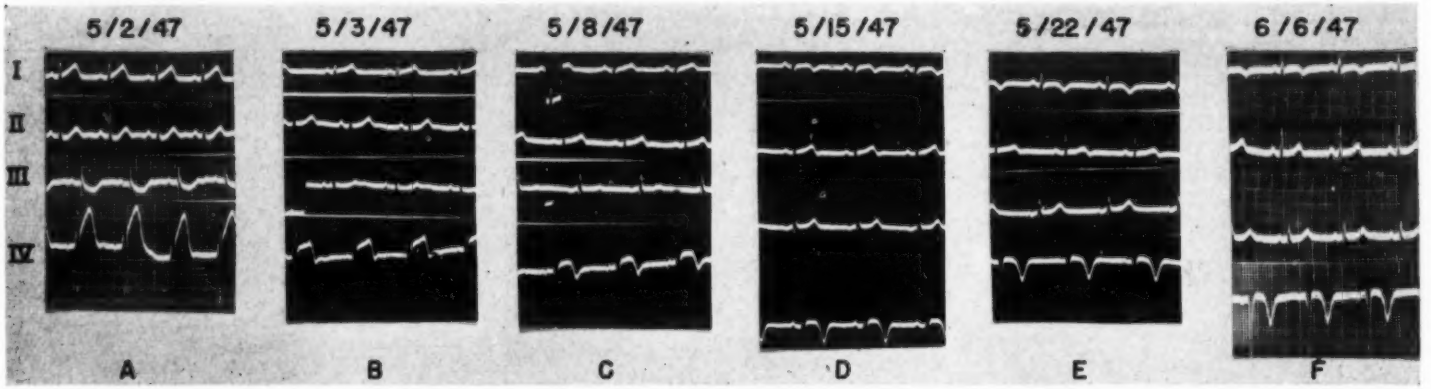


Fig. 2.—Case 4. *A*, Acute coronary thrombosis with myocardial infarction of anterior wall; pretreatment. *B*, $T_2$ is less depressed and $T_4$ is nearer isoelectric level. *C*, Tracing after seven days of therapy. *D*, Healing anterior myocardial infarction thirteen days after onset. *E*, Definite healing of infarct. *F*, Healed coronary thrombosis with infarction thirty-four days after onset; treated with a total of 2,350 mg. heparin/Pitkin menstruum over a period of twenty-six days.

days. She is presently, some sixteen months after the acute attack, free of all subjective pain and there has been almost complete amelioration of the effort syndrome. As a result of this improvement she has been able to resume partial duties as a housewife.

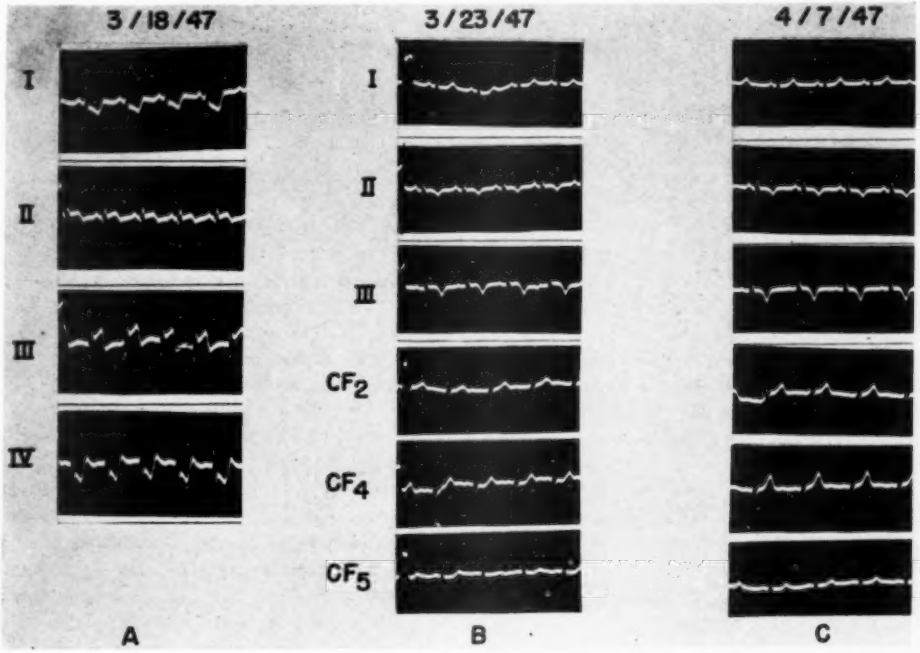


Fig. 3.—Case 6. *A*, Pretreatment extension of acute coronary thrombosis (posterior wall infarction) in hypertensive, diabetic woman, following six weeks of bed rest. *B* and *C*, Subsequent tracings five and twenty-two days following start of heparin/Pitkin menstruum therapy, showing residual posterior wall myocardial lesion.

Case 8.—H. B., a 59-year-old white man, a plumbing contractor, was first seen six months after the original myocardial infarction. This attack, which was substantiated electrocardiographically, was treated at home with bed rest and the usual medication. After six weeks in bed, he developed thrombophlebitis of the left lower extremity which was followed by another severe attack of precordial pain. He was treated at home with Dicumarol and penicillin, despite which he had recurrent pulmonary embolizations. The patient was thereupon hospitalized for bilateral femoral vein ligation following which he continued to run a persistent low-grade temperature. Adequate Dicumarol therapy and large doses of penicillin were administered throughout the entire hospital stay. On the day after discharge from the hospital he had recurrence of the thrombophlebitis involving both lower extremities with complicating massive pulmonary embolization. The patient was seen at home on Aug. 9, 1946, at which time he was given a deposit of 350 mg. of heparin/Pitkin menstruum and referred immediately to the Jewish Hospital. An admission electrocardiogram was indicative of a recent posterior wall infarction superimposed on old myocardial damage. He was given a total of 2,600 mg. of heparin divided into eight deposits over a period of eighteen days, during which time he made satisfactory progress, clinically and electrocardiographically. There were no further thromboembolic episodes and the patient was allowed out of bed after nineteen days of bed rest. The patient has been given modest periodic prophylactic deposits of heparin for the past year, during which time he has felt perfectly well and has been able to resume his occupation as a plumbing contractor.

*Comment.*—This patient is an exquisite thrombophiliac who suffered two attacks of acute coronary thrombosis and recurrent thrombophlebitis with repeated pulmonary embolizations. Dicumarol and femoral vein ligation failed to control the thromboembolic complications. Immediately after the initial deposit of heparin/Pitkin menstruum, extension of the coronary artery thrombosis was obviated and the thromboembolic complications were controlled. The response to the curative heparin/Pitkin menstruum therapy was most gratifying and throughout the prophylactic program there were no further thrombotic incidents.

CASE 10.—M. R. B., a 43-year-old, obese white physician, was first admitted to the Jewish Hospital of Brooklyn on Nov. 25, 1944. Five months prior to this admission he had a thrombophlebitis of the right leg for which the right femoral vein was ligated. Two weeks before this admission he had an episode of hemoptysis with elevation of temperature which was diagnosed as pulmonary infarction. He was hospitalized when the chest pain, cough, and fever continued and he developed signs of pleural effusion in the left pleural cavity. During this hospital stay he developed migratory thrombophlebitis of the left lower extremity with a rise in temperature. With conservative therapy all symptoms and signs abated and he was permitted to go home. Three days before the present admission, April 4, 1947, the patient was seized with a most agonizing attack of substernal pain of several hours' duration. This was obviously due to an acute myocardial infarction which an electrocardiogram showed to be of the posterior wall variety. Two days later he developed temperature and experienced pain at the base of the left lung. This pain persisted to the day of admission, and in view of the corroborative physical findings, was attributed to pulmonary infarction. A short pleuropericardial friction rub was heard at the left border of the heart. The admission electrocardiogram substantiated the diagnosis of acute posterior wall infarction. Anticoagulation therapy was instituted at once and he received a total of 1,900 mg. of heparin in the Pitkin menstruum distributed over nine deposits given over a period of thirty-two days. Although the patient was an extreme thrombophiliac, he was also a hyperreactor and obtained excellent heparin responses from relatively small doses (100 to 200 milligrams). The heart sounds, which originally were of only fair quality, improved. There were no further thromboembolic episodes and the patient was permitted out of bed less than four weeks after onset. He was placed on a prophylactic heparin program with satisfactory results to date.

*Comment.*—This obese thrombophiliac, who had recurrent attacks of thromboembolic disease despite vein ligation, suffered a third attack of acute coronary artery thrombosis. He was a heparin hyperreactor and maintained satisfactory anticoagulation effects with modest doses of heparin/Pitkin menstruum. The response to the treatment program was noteworthy, so much so that he has now resumed the practice of ophthalmology.

CASE 12.—S. L., a 47-year-old white man, a designer by occupation, was admitted to the Jewish Hospital of Brooklyn on June 12, 1947. This patient with atherosclerotic cardiovascular disease and parkinsonism had an acute attack of coronary artery thrombosis about one year prior to his present admission for which he was treated with the customary six weeks of bed rest. Ten days before admission he sustained trauma to the left tibia. Several days later he had pain in the left popliteal fossa which lasted twenty-four hours. Six days prior to admission he developed pain in the left chest which was sudden in onset and associated with dyspnea and shock. A diagnosis of coronary thrombosis with myocardial infarction was made and the patient put at bed rest. Two days later he developed a second episode of left axillary chest pain with severe dyspnea and was told that he had developed pneumonia which, however, did not respond to penicillin therapy. On the day of admission, the patient was in partial collapse, dyspneic, and cyanotic. The heart sounds were distant and there was a diastolic gallop rhythm with an impure first sound; congestive râles were audible over the posterior aspect of the lungs. The blood pressure was 106/60, as contrasted with his usual pressure of 170/90. The diagnosis was thromboembolic disease complicating acute coronary thrombosis with myocardial infarction. The presence of a posterior wall lesion was borne out by electrocardiograms taken on, and subsequent to, admission. The prognosis was considered to be extremely grave and, because of the advanced condition, prompt recourse was had to anticoagulation therapy as the only possible remedial measure. Heparin/Pitkin menstruum therapy was inaugurated immediately and continued for a period of twenty-five

days, a total of 3,200 mg. being administered in nine deposits. His response was spectacular and he was allowed out of bed on the nineteenth hospital day. He became ambulatory without much difficulty and was discharged from the hospital on the twenty-sixth day.

*Comment.*—This patient with atherosclerotic cardiovascular disease and parkinsonism was diagnosed originally as having an acute coronary artery thrombosis with a supposed complicating bronchopneumonia. The clinical picture on admission suggested pulmonary embolization complicating the coronary thrombosis and explained the ineffectiveness of penicillin therapy. The patient was in a deplorable condition. Heparinization was immediately started and continued for twenty-one days without the simultaneous administration of penicillin. This patient illustrates the effectiveness of the treatment in curtailing the period of bed rest, only nineteen days being required, as against a customary minimum of six weeks in a case of this gravity.

CASE 13.—P. B., a 52-year-old white housewife, was known to have hypertension for many years with a systolic blood pressure of 240 millimeters of mercury. Six years prior to her admission to the Jewish Hospital of Brooklyn, Nov. 19, 1946, on the service of Dr. E. L. Shlevin, she began to complain of occasional precordial oppressive pain with radiation to the left arm. Soon afterward she was confined to bed for approximately sixteen weeks because of acute myocardial infarction, during which time she sustained a bilateral thrombophlebitis. Three years afterward she had a second coronary artery occlusion. Four days before hospitalization she had typical signs of acute coronary closure with shock, precordial pain, apprehension, and precipitate drop in blood pressure. The clinical diagnosis was confirmed by electrocardiographic evidence which indicated an acute posterior wall infarction (Fig. 4). Her systolic blood pressure, which was usually around 240, was now 120 mm. Hg, and there was slight elevation of temperature and leucocytosis. Twenty-four hours after admission she exhibited a right hemiplegia attributed to embolization from an intracardiac mural thrombus. The patient became confused and uncooperative, and the prognosis appeared extremely grave. The next day she had severe precordial pain and developed a protodiastolic gallop rhythm and it was felt that she had sustained a pulmonary embolus. Twenty-four hours later she had pain in her right leg and presented the clinical features of an acute thrombophlebitis. Within a period of seven days, the patient had acute coronary artery thrombosis, cerebral embolization, and right thrombophlebitis. Her condition was grave and recourse was had to anticoagulation therapy. Twenty-four hours after the first deposit of 450 mg. of heparin in the Pitkin menstruum the patient had a partial return of speech. It will be noted that the initial dose was 450 mg. instead of the usual 350 to 400 mg. because of the condition of the patient and the extent of thrombotic involvement. She was treated intensively for twenty-three days with a total of 2,650 mg. of heparin divided into eight subcutaneous deposits, and her condition improved in a most satisfactory manner. Thereafter, and until discharge, she was placed on periodic, reduced (150 mg.) maintenance dosages of heparin for prophylaxis. She began to regain almost complete use of her extremities, recovered her speech, became less confused and more cooperative, and eventually was permitted out of bed on the twenty-ninth day of heparin therapy. In all, the patient was given eleven deposits of heparin/Pitkin menstruum for a total of 3,200 mg. over a period of thirty-five days, after which she was able to leave the hospital. She could walk unaided, and except for residual mild facial paralysis, her condition was most satisfactory.

*Comment.*—Within seven days this patient exhibited coronary artery thrombosis with myocardial infarction, cerebral artery embolization from an intracardiac mural thrombus, and venous thromboembolic disease with pulmonary embolization. She is an extreme example of thrombophilia with a background of hypertensive atherosclerotic cardiovascular disease. She was almost moribund prior to treatment and progressed favorably from the very outset of therapy. The extension of the coronary artery thrombosis was averted, all complicating thromboembolic episodes were prevented, and restoration of the vascular stream in the occluded vessels was promoted. The treatment program was intensified because of the widespread nature of the process. Attention is called to the fact that the major response was evident within the twenty-three days of intensive therapy.

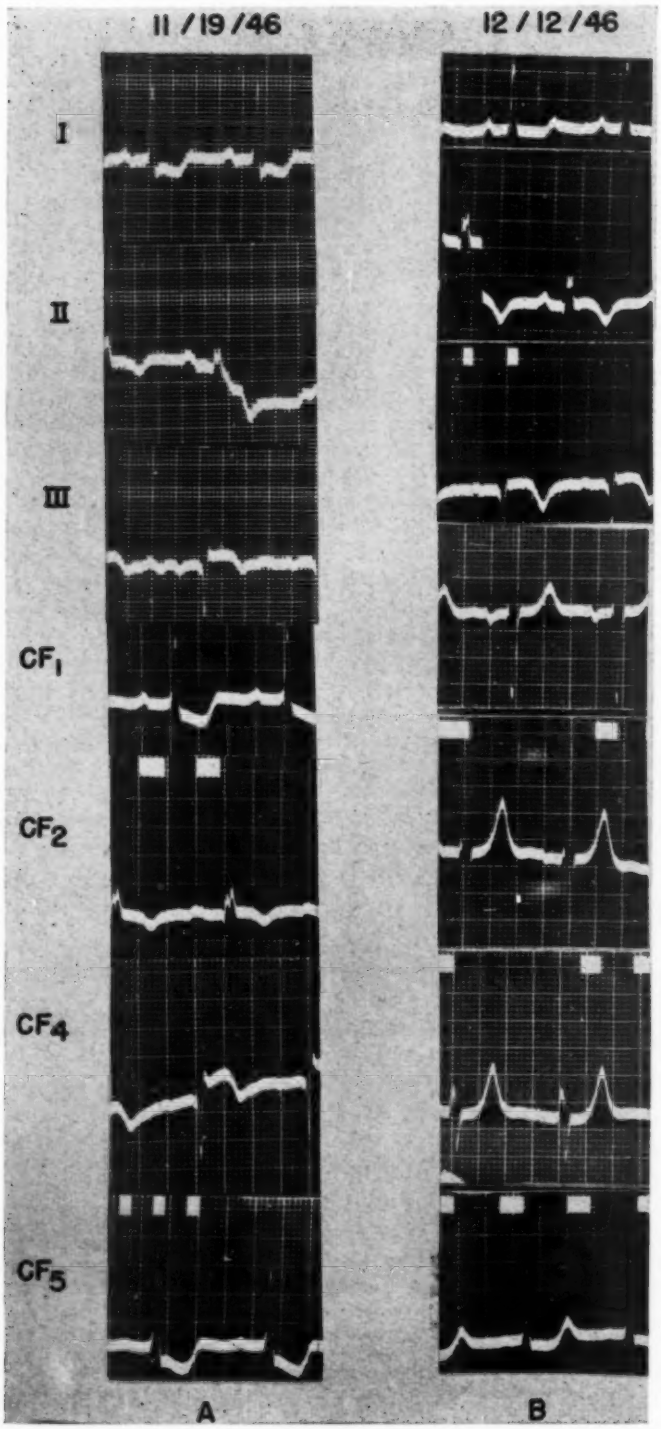


Fig. 4.—Case 13. *A*, Acute posterior wall infarction with some anterior wall involvement; followed by cerebral embolus with hemiplegia, pulmonary embolus, and thrombophlebitis. Patient in coma and moribund at start of therapy. *B*, Electrocardiogram twenty-four days later showing return toward normal. Satisfactory recovery after twenty-three days of intensive heparinization.

CASE 16.—B. T., a 59-year-old white man, was a known hypertensive for the previous eight to nine years but had always been asymptomatic except for occasional headaches. Forty hours prior to his admission, the patient was awakened at night with a burning substernal pain associated with epigastric distress. The pain radiated through to the back of the chest and left shoulder. He walked around that day and consulted his local physician that night, at which time an electrocardiogram revealed auricular flutter. He was admitted to the Jewish Hospital on July 16, 1946,

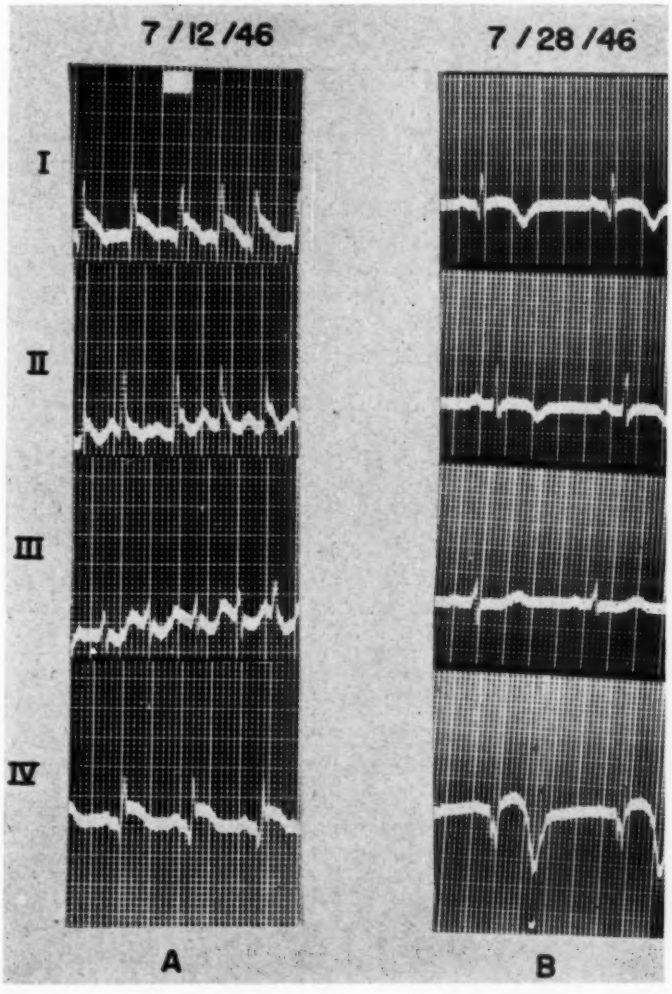


**Fig. 5.—Case 16.** *A*, **Auricular flutter eighteen days before institution of therapy.** *B*, **Acute anterior wall infarction three days before institution of therapy. In the interim patient sustained thrombophlebitis and pulmonary embolization. No further thromboembolic episodes after start of heparinization.**

service of Dr. E. L. Shlevin, with a temperature of 100.5°F., a pulse rate of 90, and respirations of 24 per minute. The systolic blood pressure, ordinarily over 200, was now 160 millimeters of mercury. He was in severe pain and distress with cyanosis of the lips and nails. He had a trigeminal rhythm for which quinidine therapy was prescribed. The electrocardiogram (Fig. 5) on admission again disclosed auricular flutter. The next day he had severe precordial pain with a heart rate of 160

per minute. He was given oxygen, morphine, and atropine with some relief. The cardiac irregularity continued the next day and the dosage of quinidine was increased. Twenty-four hours later he had bilateral calf tenderness which disappeared spontaneously. Two weeks after admission he was awakened with sudden pain in the right anterior chest which became excruciating on deep inspiration. It was fairly evident that the patient had sustained a pulmonary embolization. The next day anticoagulation therapy was begun with heparin/Pitkin menstruum. Two days later he still had marked chest pain over the right lower lobe on inspiration; a bedside roentgenogram of the chest was negative (it was impossible to obtain the oblique views necessary to properly visualize early pulmonary infarction). Eight days after the beginning of anticoagulation therapy his general condition was much improved; the temperature was normal, but he still had dullness over the right posterior lung base with a pleural friction rub. An interim electrocardiogram (Fig. 5, *B*) showed a recent anterior wall infarction with no evident quinidine effect. The patient continued to make satisfactory progress and eleven days after heparinization was started the entire chest was clear. Four days later he was allowed to sit in bed and several days afterward he was permitted out of bed, at which time he had no complaints. A total of 2,850 mg. of heparin/Pitkin menstruum was given in nine deposits over a period of twenty-four days.

*Comment.*—This patient had multiple thromboembolic complications associated with the original coronary thrombosis over a period of two weeks, during which time he was treated with the conventional methods of therapy. It was only after the institution of anticoagulation therapy with heparin/Pitkin menstruum that the thromboembolic episodes were arrested. He had no further clot propagation or embolizations.

## DISCUSSION

Coronary artery thrombosis offers a very attractive field for anticoagulation therapy. Reports have already appeared which indicate that this form of therapy holds great promise.[15-19] A triphasic therapeutic attack is admittedly indicated in coronary artery thrombosis. The first and most important objective is to prevent central propagation of the thrombus from what, in many instances, is merely an occlusive involvement of a small twig of a coronary vessel. In this manner it is possible to limit the degree of myocardial infarction and resultant myocardial damage. All too often the propagation thrombus is the lethal factor. The second objective is the prevention of embolization from mural thrombi secondary to the myocardial infarction. The third phase of the therapy is levelled at the not infrequent complicating thrombosis of deep venous channels resulting from slowing of the vascular stream in the bedridden convalescent patient; the subsequent, at times ominous, pulmonary embolizations may be clinically confusing. For optimum effects the immediate administration of anticoagulation therapy is essential. One cannot advocate too strongly that the prompt inauguration of this therapy may be life saving and, of course, serves to minimize the ultimate damage.

In 1940 Best[20] suggested that the clinical cardiologist explore the possibilities of heparin in acute coronary thrombosis. Despite early encouraging results, this treatment approach was abandoned primarily because of the technical difficulty of administering heparin in its aqueous form, especially in cardiac cases. The anticoagulation treatment approach was revived by Nichol and Page,[16] Peters, Guyther, and Brambel,[17] Wright,[18] and Parker and Barker[19] when Dicumarol became available for clinical use.

Recourse to Dicumarol is understandable because it can be administered orally. The effectiveness of the drug, however, is tempered by the difficulty

in planning dosage schedules and, more important, because of its occasional dangerous complications.[21,22,23] There is considerable variability in the response to Dicumarol, this lack of uniformity of response being present even in the same individual. Fixed dosage schedules cannot be established; patients must be individualized. The action of Dicumarol is slow, twenty-four hours or longer being required before its therapeutic effectiveness is achieved. Because of this delay in action and the variability of the patient's response, the drug is not useful in the early, critical stages of coronary thrombosis. Patients receiving Dicumarol require daily prothrombin determinations. The use of Dicumarol should not be countenanced unless there are proper laboratory facilities for prothrombin determinations by acceptable techniques. The latter are time consuming and relatively expensive.

Unlike heparin, the presence of liver and/or kidney disease militates against the use of Dicumarol. This is a disadvantage in patients with coronary thrombosis who so often have generalized atherosclerotic cardiovascular disease with renal involvement. Dicumarol has been attended with irreversible hemorrhage and death.[24] Transfusions of fresh blood alone do not always arrest the hemorrhagic tendency occasioned by the drug. Massive dosages of vitamin K are required which may, occasionally, reinduce thrombosis.[25]

In summary, then, the delayed action, contraindications, potential hazards, the unpredictable treatment failures, and the requisite, complicated, but indispensable laboratory procedures militate against Dicumarol as the anticoagulant of choice in coronary artery thrombosis. Furthermore, although the technical difficulties and hazards of administering Dicumarol are recognized and have been surmounted to some extent, the drug is not an effective agent during the initial, critical phase of acute coronary artery thrombosis. In addition, the use of Dicumarol presents difficulties in the attempt to carry out a protracted, prophylactic anticoagulation program. The relative merits of heparin and Dicumarol are compared in Table II.

The properties of heparin which render it uniquely applicable in thromboembolic disease are that it prevents, with the aid of a plasma cofactor, the conversion of prothrombin to thrombin; it forms with serum albumin a strong antithrombin; and, finally, it prevents the formation of thromboplastin from platelets.[26] The properties of heparin predicate the fact that a clot, regardless of its site or stage, cannot propagate in the presence of heparin. However, what happens to the clot which is already present?

It has been possible to determine experimentally at what stage of clot formation heparin administration results in solution of the clot and what effects heparin has on the organizing clot.[3-11]

Briefly, studies on the effect of heparin on experimental thrombosis have yielded the following data:

1. Red cell clots which are not organized and contain a minute amount of fibrin (sludge stage) disappear completely under heparin therapy.

2. Heparin therapy maintains patent adjacent collaterals and tributaries which ordinarily would become involved in the thrombotic occlusive process. The compensatory collaterals often become as large as the originally occluded

vessel. This phenomenon has not been observed in control veins. It may be assumed, though not necessarily proved, that these processes also occur in obstructed lymphatics.

TABLE II. COMPARISON OF THE ADVANTAGES AND DISADVANTAGES OF HEPARIN/PITKIN MENSTRUUM AND DICUMAROL

| | HEPARIN/PITKIN MENSTRUUM | DICUMAROL |
|---|---|---|
| Dosage | Initial dose 400 mg.; thereafter, 300 to 400 mg. as indicated. | No standard dosage; completely dependent upon daily prothrombin determinations |
| Control | Simple coagulogram at bedside | Daily precise prothrombin time determined in laboratory |
| Response | Prompt anticoagulant response within 1 to 2 hours; consistent and predictable; each injection effective for 48 hours or longer | Lag in effect for 24 hours or longer; unpredictable response necessitating individualization of dosage schedule |
| Administration | Subcutaneous; advantage only in moribund cases | Oral; advantage except in comatose patients |
| Contraindication | Active bleeding | Active bleeding, renal disease, hepatic disease |
| Clinical use | All venous and acute arterial thromboembolic disease | Lag effect of Dicumarol necessitates initial conjoint use of heparin in acute arterial lesions |
| Complications of overdosage | None with intact cardiovascular system | Hemorrhage |
| For interruption of therapy | 1. Ice bag to site of heparin deposit<br>2. Small whole blood transfusion<br>3. Protamine, intravenously* | 1. Vitamin K intravenously (may reinduce thrombosis)<br>2. One or more 250 to 500 c.c. whole fresh blood transfusions |

*The use of protamine has never been required in the course of several thousand deposits of heparin/Pitkin menstruum.

For abrupt termination of progression of the initial thrombotic process, which is the most urgent objective, heparin is the anticoagulant of choice. Heparin in the Pitkin menstruum, because of its effectiveness, prompt action, and simplicity of administration, appears to be the preparation best suited for the treatment of acute coronary artery thrombosis.

While this series is much too small to permit detailed statistical analysis, a conservative review of mortality and morbidity data is enlightening in view of the almost uniform gravity of the twenty patients comprising the group.

A generally poor pretreatment prognosis was justified in this group for the following reasons:

1. Only three (15 per cent) of the twenty patients had an initial, uncomplicated attack of coronary artery thrombosis. While it is ordinarily hazardous to predict the outcome in this type of case, all three patients (Cases 2, 4, and 5) were relatively young; all had extensive myocardial infarction; and all were desperately ill. The clinical and electrocardiographic picture warranted an ominous

prognosis in all three patients. Recovery with minimum residue in all three may be attributed in part to the early administration of anticoagulation therapy, four, nine, and twelve hours, respectively, after onset of the attack.

2. Nine patients (45 per cent) had antecedent attacks of coronary artery thrombosis. These patients with a previously compromised coronary artery tree had an increasingly unfavorable outlook. This is especially true of the six patients who, in addition, had complicating thromboembolic episodes. The treatment program may well have been an important factor in the recovery of all nine of these patients.

3. A total of fourteen (70 per cent) patients had one or more complicating thromboembolic episodes. Four had arterial embolizations from mural intracardiac thrombi; three of these had, in addition, venous thromboembolic disease. Of the latter, Case 15 (our only treatment failure, first seen in a moribund state eleven days after the coronary occlusion) succumbed to the combination of anterior wall infarction, auricular fibrillation, cerebral embolization, pulmonary edema, thrombophlebitis, and massive pulmonary embolization. Case 13 with an almost identical clinical syndrome made a spectacular recovery despite multiple arterial and venous thromboembolic episodes over a period of seven days. Ten patients had pulmonary embolizations, at times multiple, mostly from peripheral vein thrombosis.

It is interesting to collate the mortality figures in cases of a comparable nature. The average mortality of uncomplicated acute coronary artery thrombosis varies from 20 to 30 per cent.[18] Of the twenty patients in our series, six were in this category and all recovered. This is suggestive, but inconclusive because of the limited number of patients. More significant is the estimated 60 to 70 per cent mortality for coronary artery thrombosis with complicating thromboembolic phenomena,[18] which compares with one treatment failure (7 per cent) in the fourteen patients comprising the group of complicated cases.

An analysis of the morbidity, clinical picture, and progress of both the uncomplicated and the complicated cases during and after the treatment program is revealing. In the absence of anticoagulation therapy, an unpredictable number of these desperately ill patients might conceivably have sustained increase in the area of myocardial infarction as a result of propagation of the thrombus in the occluded coronary artery, or secondary coronary occlusions with resultant multiple infarctions. Furthermore, there was every reason to believe that some of the uncomplicated cases would develop embolic phenomena from intracardiac mural thrombi. Finally, a majority of the patients already exhibiting thromboembolic phenomena would inevitably continue to suffer thromboembolic episodes with less and less hope of survival.

While some of the foregoing is conjectural, the fact remains that in none of the nineteen patients who recovered was there any evidence of extension of preexistent thrombus, arterial, intracardiac, or venous, once anticoagulation therapy was instituted. Furthermore, all thromboembolic processes were terminated promptly. When anticoagulation therapy with heparin/Pitkin menstruum was inaugurated early, there was suggestive delimitation of myocardial damage with more rapid clinical and electrocardiographic regression. In the optimally treated

patients, the span of bed rest was reduced conspicuously, the convalescence was accelerated, and the patients were restored more rapidly to their accustomed activities.

These patients presumably have an inherent clotting tendency and are subject to recurrent episodes of thrombosis. For this reason, after the intensive treatment for the acute thrombotic process has been completed, they are now given a maintenance prophylactic program with modest dosages of heparin/Pitkin menstruum while they are ambulatory and for an indefinite period of time. This prophylactic program was originally suggested by the ease with which heparinization was continued and accomplished for long periods of time in ambulatory patients who were up and about following severe venous thromboembolic disease. Patients were encountered repeatedly who required dosages of 300 to 400 mg. of heparin in the Pitkin menstruum every other day in order to effectuate adequate coagulograms during the active phases of the disease. These same patients, when there was no longer any detectable evidence of the persistency of thrombosis, could then be maintained in a protected state on as little as 100 mg. of heparin in the Pitkin menstruum deposited every second to seventh day or longer. This spacing permitted the patients to be treated as ambulatory subjects without inconvenience. There apparently is a direct relationship between the mass and extent of thrombosis and the degree of response to heparin; as the clots disappear, the individual becomes less resistant and more responsive to the anticoagulant. The detailed technical aspects of this program and the results of this prophylactic study will be the subject of a forthcoming report.

While expansion of this project to include a sufficiently large number of cases for statistical purposes is necessary to establish unequivocally the virtues of anticoagulation therapy in acute coronary artery thrombosis and its complications, the gratifying response of this small series of profoundly ill patients would seem to indicate that heparin/Pitkin menstruum, because of its simplicity of administration, prompt effectiveness, and absence of toxicity, is well suited for the treatment of this serious disease.

## SUMMARY AND CONCLUSIONS

1. Anticoagulation therapy with heparin/Pitkin menstruum was the subject of an exploratory study in twenty consecutive, unselected patients with acute coronary artery thrombosis and myocardial infarction.

2. The treatment program and its rationale in acute coronary thrombosis is discussed.

3. All of the patients in the series were seriously ill; some were desperately ill. Fourteen of the patients (70 per cent) had clinically detectable, complicating thromboembolic episodes. One of these complicated cases represented the only treatment failure (5 per cent) in the series of twenty patients.

4. In none of the nineteen patients who recovered was there evidence of thrombus propagation, once anticoagulation therapy was instituted. Furthermore, all complicating thromboembolic processes were promptly terminated.

5. In the optimally treated patients the span of bed rest was conspicuously reduced. Convalescence was accelerated and the patients were restored more rapidly to their accustomed activity.

6. The gratifying response of this small, though representative series of gravely ill patients would seem to indicate that heparin/Pitkin menstruum, because of its simplicity of administration, prompt effectiveness, and absence of toxicity, is well suited for the treatment of acute coronary artery thrombosis and its complications.

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# IV. CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN INFARCTION OF THE INTERVENTRICULAR SEPTUM AND RIGHT VENTRICLE

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FROM pathologic studies, it is well known that infarction of the interventricular septum usually accompanies infarction of the free anterior wall of the left ventricle, often occurs in association with infarction of the free posterior wall, and occasionally develops as a primary lesion. Nevertheless, little or no attention has been devoted to the diagnosis of septal infarction in the current textbooks and monographs on electrocardiography. However, there are several reports of electrocardiographic studies in patients with pathologically proved or clinically presumptive septal infarction.

Auriculoventricular block is a well-documented complication of septal infarction. In a series of 375 cases of coronary occlusion, Master, Dack, and Jaffe[1] found prolongation of the P-R interval beyond 0.20 second in 10 per cent, second degree block in 2.4 per cent, and complete block in 1.6 per cent. The incidence of partial and of complete auriculoventricular block in this series corresponded closely with the averages in a group of 1,500 cases collected from the literature. High-grade partial and complete block were attributed to involvement of the auriculoventricular node secondary to infarction of the septum, but simple prolongation of the P-R interval could not be correlated with any specific anatomical lesion. The septal lesion responsible for severe auriculoventricular block was almost invariably associated with posterior infarction and only rarely represented an extension from anterior infarction. This finding corresponded with gross observation that the blood supply of the auriculoventricular node is derived from the right coronary artery in 92 per cent and from the left in 8 per cent of the hearts.

Prolongation of the QRS interval is another recognized manifestation of septal infarction. The incidence of this finding was 43 per cent in thirty patients with subsequent pathologic demonstration of infarction which extended into the septum, and was 21 per cent in nineteen patients with infarction which spared the septum.[2] However, an insufficient number of leads was obtained in these cases to localize accurately the conduction defect and thus to determine its relation to the anatomical lesions.

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Wilson and associates[3,4,5,6] demonstrated the need for multiple precordial leads for localization of the site of an intraventricular conduction defect and for the differentiation of defects due to septal infarction from those due to other causes. Conduction defects in the right side of the septum and right ventricle were recognized by the presence of a late intrinsicoid deflection in leads from the right precordium which faced these structures.[3] Right bundle branch block due to septal infarction was differentiated from that due to other causes by the direction of the initial phase of the QRS complex in these leads. Uncomplicated right bundle branch block was manifested by an initial R wave, a subsequent downstroke or coarse slurring, and a secondary late upstroke,[3] whereas right bundle branch block associated with septal infarction was characterized by an abnormal Q wave and a late R wave in these leads.[4,5,6] Section of the right branch of the bundle of His in dogs resulted in a primary and a secondary late R wave in leads from the right precordium, and subsequent septal infarction produced by ligation of the septal branch of the left coronary artery led to the replacement of the initial upstroke by an abnormal Q wave.[7] Thus, the initial R wave was derived from septal activation and was obliterated and replaced by a Q wave in the presence of extensive septal infarction.

Conduction defects in the left side of the septum and free wall of the left ventricle were recognized by the presence of an abnormally late intrinsicoid deflection in leads from the left precordium and axilla which faced these structures.[3] The site of the conduction defect in the left ventricle was indicated by the direction of the first phase of the QRS complex in these leads. When an initial R wave and late intrinsicoid deflection were recorded in left ventricular leads, the QRS prolongation was attributable to left bundle branch block.[3] This initial R wave persisted when left bundle branch block was complicated by anterolateral infarction. As a consequence, diagnostic signs of infarction were not present under these circumstances. When an abnormal Q wave and late intrinsicoid deflection were recorded in leads from the left precordium, the prolongation of the QRS complex was most likely due to delay in passage of the impulse through the free wall of the left ventricle secondary to infarction of the subendocardial portion.[6] However, QS deflections were recorded in left ventricular leads in one case of left bundle branch block as a result of the combination of a massive transseptal and extensive anterolateral infarction.[8]

The QRS interval may be of normal duration in the presence of extensive transseptal infarction, even when complicated by perforation of the septum.[9-12] Nevertheless, abnormalities in the QRS-T pattern suggestive or diagnostic of septal infarction may be detectable in precordial leads facing the right ventricle and right side of the septum in the absence of a conduction defect. The normal R wave in these leads is produced largely by activation of the septum and, partially, by activation of the outer wall of the right ventricle.[13,14] Kossmann and De La Chapelle[15] recorded QS complexes at positions over the right ventricle in a patient with anteroseptal infarction proved at necropsy and attributed the absence of the normal R wave from these leads to the lesion of the anterior portion of the septum. Pardee and Goldenberg[16] observed a transient QS complex and coronary T wave in Lead IVF in a case with infarction localized to the

anterior portion of the septum. Roesler and Dressler[17] reported five cases with pathologic evidence of extensive infarction of the septum, continuing into the anterior and posterior walls of the left ventricle. These were manifested electrocardiographically by signs of anterior infarction in the precordial and signs of posterior infarction in the limb leads. Their studies suggested that a diagnosis of infarction of the interventricular septum, as well as of the anterior and posterior walls of the left ventricle, may be made when the electrocardiogram reveals evidence of coexistent anteroposterior infarction.

In a previous communication,[18] two types of QRS pattern in right ventricular Leads $V_1$ and $V_2$ were correlated with the septal portion of an anteroseptal infarct found at autopsy, namely, (1) QS complexes which were shown to be abnormal rather than normal variants, either by the association of RS-T segment displacement typical of recent infarction or by the demonstration of an initial R wave in leads farther to the right, such as Lead $V_{3R}$; (2) an initial Q wave, followed by a small R wave and a deep S wave.

A similar method of electrocardiographic and pathologic examination is employed in the present study and all cases in which infarction was demonstrated at autopsy in one-third or more of the interventricular septum are included, except for thirteen cases of localized anteroseptal infarction summarized previously.[18] The material comprises six cases in which the infarction was primary in and largely confined to the septum, fifty-nine cases in which the septal lesion was associated with a large anterior or anteroposterior infarction, and twenty-four cases in which it was associated with posterior infarction. Significant septal involvement was thus found at autopsy in a total of 102 cases, or 63 per cent of the series of 161 cases upon which these reports are based. Eighteen cases are reported in detail in this communication and the findings pertaining to the septal lesion in the remainder are classified and summarized.

Continuation of infarction of the left ventricle and septum into the right ventricle is generally regarded as uncommon,[19,20] but was found in one-third of the cases by Bean[21] and by Feil, Cushing, and Hardesty.[22] Electrocardiographic patterns due to human right ventricular infarction have not been clearly defined, because of (1) the difficulty in differentiating the effects of the right ventricular extension from those of the primary left ventricular and septal lesion, and (2) the extreme rarity of infarction confined to the right ventricle. Electrocardiographic signs of posterior infarction were reported in three patients with subsequent pathologic demonstration of infarction limited to the right ventricle and septum.[22,23,24] In animals with experimental infarcts of the right ventricle, QS complexes and displacement of the RS-T segment were recorded in leads from the overlying epicardium,[25] which were similar to those registered through direct leads from the surface of a transmural left ventricular infarct. The reason for the obliteration of the initial upstroke of septal derivation in these animals was not apparent. Since septal infarction in human beings may be manifested by abnormal QS complexes and displacement of the RS-T segment in precordial leads over the right ventricle,[18] great difficulty would be anticipated in the electrocardiographic differentiation of septal and right ventricular infarction.

Isolated infarction of the right ventricle was not found in this series. Extension of infarction of the anterior wall of the left ventricle across the septum into the anterior wall of the right ventricle was demonstrated pathologically in six cases and continuation of a lesion of the posterior wall of the left ventricle into the posterior wall of the right ventricle was found in thirteen cases. These nineteen cases constituted 11.8 per cent of the entire series and will be analyzed to determine the presence or absence of electrocardiographic signs referable to the right ventricular involvement.

## CASE REPORTS

CASE 69.—A 52-year-old man had had hypertension for seventeen years, but was asymptomatic until March, 1945, when he began to have dyspnea and transient epigastric fullness on exertion. He was admitted to the hospital in left ventricular failure on March 30 and promptly regained compensation. His clinical course was compatible with a small myocardial infarction. On Nov. 30, 1945, he was seized with severe protracted epigastric pain and was brought to the hospital in shock. He remained in circulatory collapse and died seven days later.

*Electrocardiographic Findings.*—Electrocardiograms from both admissions are reproduced serially in Fig. 1. The patient received 0.7 Gm. of digitalis prior to the electrocardiogram of March 31, an additional 1.9 Gm. between the first and second tracings, and 0.5 Gm. between April 9 and April 14. No cardiac glycosides were given during his second admission. All tracings taken during the first admission showed a QRS pattern typical of left ventricular hypertrophy and were characterized by a slurred R wave and late intrinsicoid deflection in Leads $V_5$ and $V_6$ and a deep, broad S wave in Leads $V_1$ and $V_2$. The coarse notching of the R wave in Lead $V_4$ was a transitional zone phenomenon. Attention is directed to the presence of an initial R wave in all precordial leads of each tracing on the first admission and to the absence of significant serial changes in the QRS pattern during this period. On the other hand, striking changes occurred in the RS-T segment and T wave in all precordial leads except Lead $V_1$. The initially inverted T waves in Leads $V_5$ and $V_6$ were less deep on April 9 and became low upright on April 14. The changes were opposite to those which would have been expected from progressive digitalization, but were compatible with those observed during recovery from left ventricular failure. The convexly upward bowing of the RS-T segment and the terminal inversion of the T wave in Leads $V_2$ through $V_4$ of the tracing of March 31 were strongly suggestive of a localized lesion in the mid-zone or subepicardial layer of myocardium and were probably independent of digitalis. A small anteroseptal infarct, a localized pericarditis, and acute right ventricular dilatation secondary to left ventricular failure were considered as possible causes of this pattern. The absence of T-wave inversion in Lead $V_1$ was strongly against acute cor pulmonale and the history was more in keeping with a very small infarct than with pericarditis. Serial changes occurred in the T waves of Leads I and II comparable to those in Lead $V_6$. Lead $V_1$ of the tracings taken during the second admission showed a tall R wave and a very late intrinsicoid deflection, beginning 0.10 second after the onset of the QRS complex, whereas Leads $V_5$ and $V_6$ exhibited a relatively early intrinsicoid deflection, beginning 0.04 second after the onset of the QRS complex, and followed by a broad, slurred S wave. These findings were diagnostic of right bundle branch block. A deep Q wave was found in Leads $V_1$ and $V_2$ in place of the initial R wave expected in leads over the right ventricle in the presence of right bundle branch block. Since this initial R wave is produced by activation of the septum, its disappearance and replacement by a Q wave constituted evidence of infarction of the septum. The initial Q wave in Lead $V_1$ represented left ventricular cavity potentials transmitted through the inert septum, and the tall late R wave was derived presumably from activation of an uninfarcted outer wall of the right ventricle over an aberrant pathway. The high voltage of the R wave was attributable to the circuitous route of activation and did not constitute evidence of right ventricular hypertrophy. The transitional zone was located near the midline in the tracing of December 1 and shifted to the left between Leads $V_5$ and $V_4$ on December 5. Thus, Leads $V_5$, $V_6$, and $V_5$ reflected the potential variations of the left ventricle,

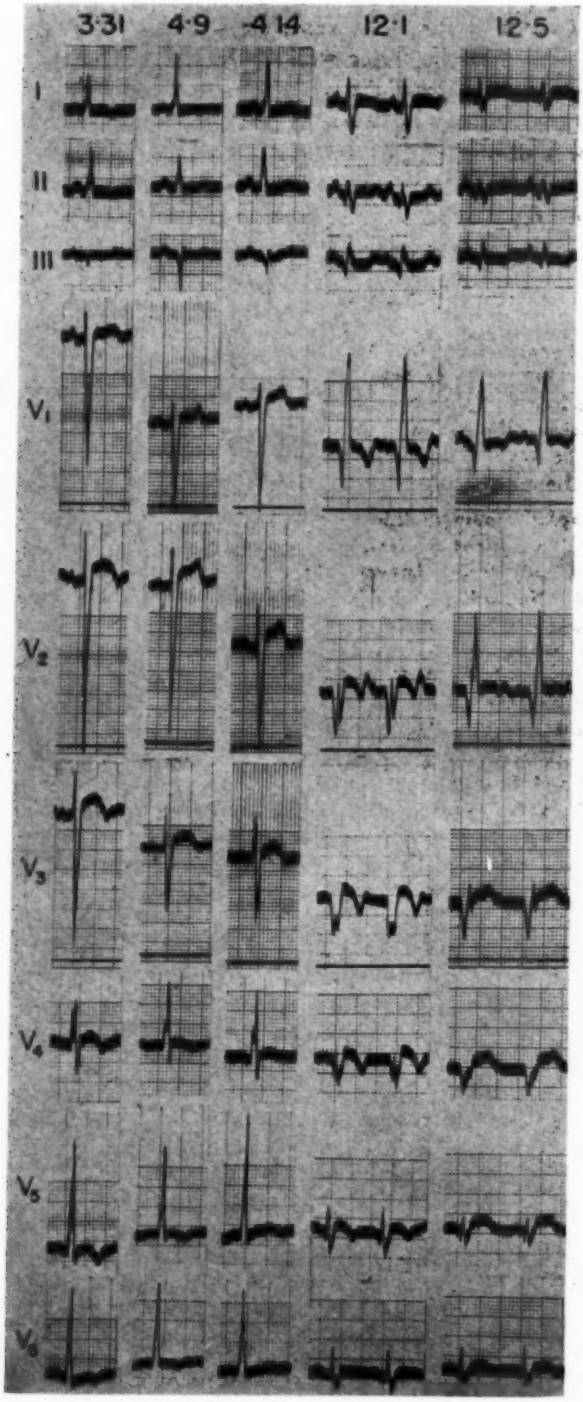


**Fig. 1.—Serial electrocardiograms in Case 69, showing evidence of small intramural anteroseptal infarction in March and large anteroposterior and septal infarction with right bundle branch block in December.**

and the abnormal Q wave and RS-T segment displacement in these leads were indicative of continuation of the septal infarct into the anterior and anterolateral walls of the left apex. The coved inverted T waves of Leads $V_1$ through $V_5$, recorded on December 1, were typical of recent infarction and their replacement by a monophasic upright T wave on December 5 was suggestive of further injury to the supepicardial layer. A triphasic QRS complex was recorded in Lead $aV_F$ and could be resolved into Q, R, and S components, each of which was slurred and approximately 2.0 mm. in amplitude. In view of the presence of right bundle branch block, the late, broad S wave indicated that Lead $aV_F$ reflected the potential variations of the posteroinferior wall of the left ventricle, and the abnormally broad, slurred Q wave signified extension of the infarct subendocardially into this region. The abnormal Q wave of Lead $aV_F$ carried over into standard Leads II and III, producing a pattern in these leads of right bundle branch block complicated by posterior infarction.

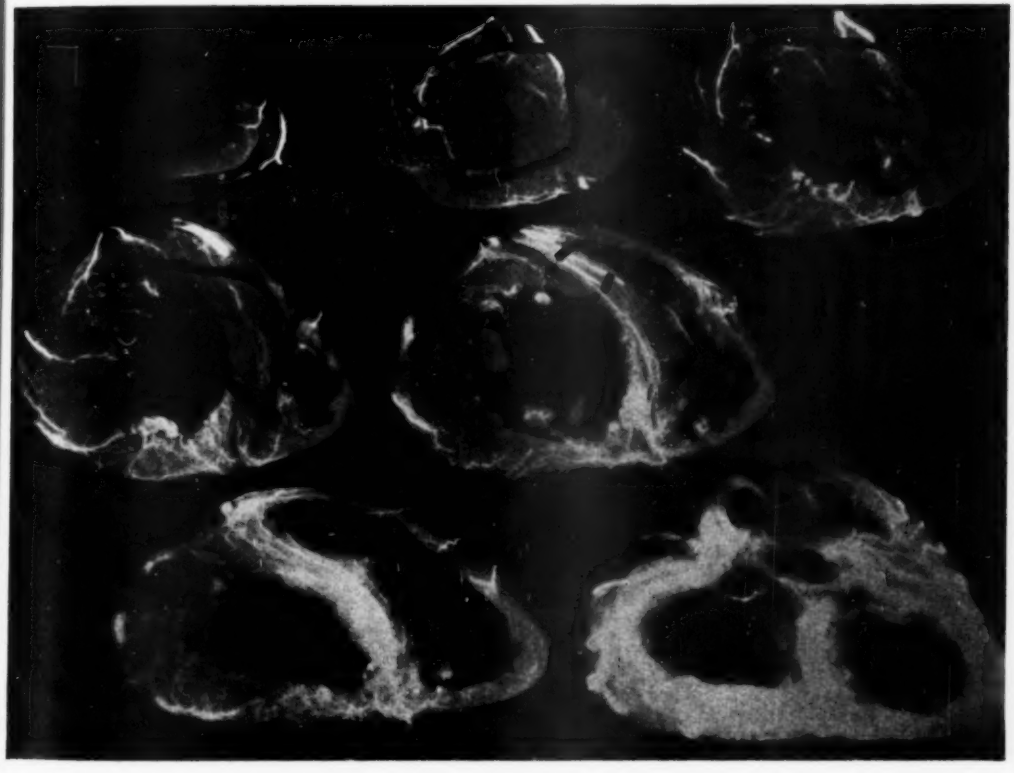

Fig. 2.—Roentgenogram of the injected heart in Case 69, showing small, healed anteroseptal infarct in broken outline and recent anteroposterior and septal infarct in solid lines.

*Pathologic Findings.*—The heart weighed 641 grams and exhibited a recent comma-shaped infarct, which involved the entire apical two-thirds of the interventricular septum and extended forward into the subendocardial two-thirds of the anterior wall and backward into the posteroapical region, as demarcated by the solid lines of Fig. 2. The free wall of the right ventricle was not infarcted. There was a small healed infarct localized in the anteroseptal wall of the fifth segment, as indicated by the broken lines. An intramural infarct in this location could have accounted for the serial changes in the RS-T segment and T wave observed in Leads $V_2$, $V_3$, and $V_4$ during the first admission and for the absence of associated changes in the QRS complex. The location of the recent infarct corresponded closely with that predicted from the electro-

cardiograms taken on the second admission. It is noteworthy that a pattern customarily regarded as right bundle branch block accompanied an infarct which destroyed the apical two-thirds of the septum, but left the basal one-third intact. The expected initial R wave in right ventricular Lead $V_1$ was replaced by a Q wave, despite the presence of histologically normal muscle in the basal one-third of the septum. The initial positive potentials which might have been referred to the right ventricular cavity from activation of the intact portion of the septum were apparently obliterated by greater negative potentials simultaneously transmitted from the left ventricular cavity through the infarcted portion of the septum. The subendocardial position of the anterolateral infarct was accurately reflected in the Q-R pattern of Leads $V_4$ and $V_5$, and the subendocardial posteroapical infarct, by the Q-R complexes of Leads $aV_F$, II, and III.

CASE 70.—A 59-year-old woman gave a four-month history of uncontrolled diabetes mellitus. During this period she began to have angina pectoris. Attacks were of brief duration until the day of admission, when she had a prolonged attack of exceptionally severe retrosternal pain and was brought to the hospital in shock. A single dose of 2.0 cat units of Digalen was given shortly after admission. Death occurred on the seventh hospital day.

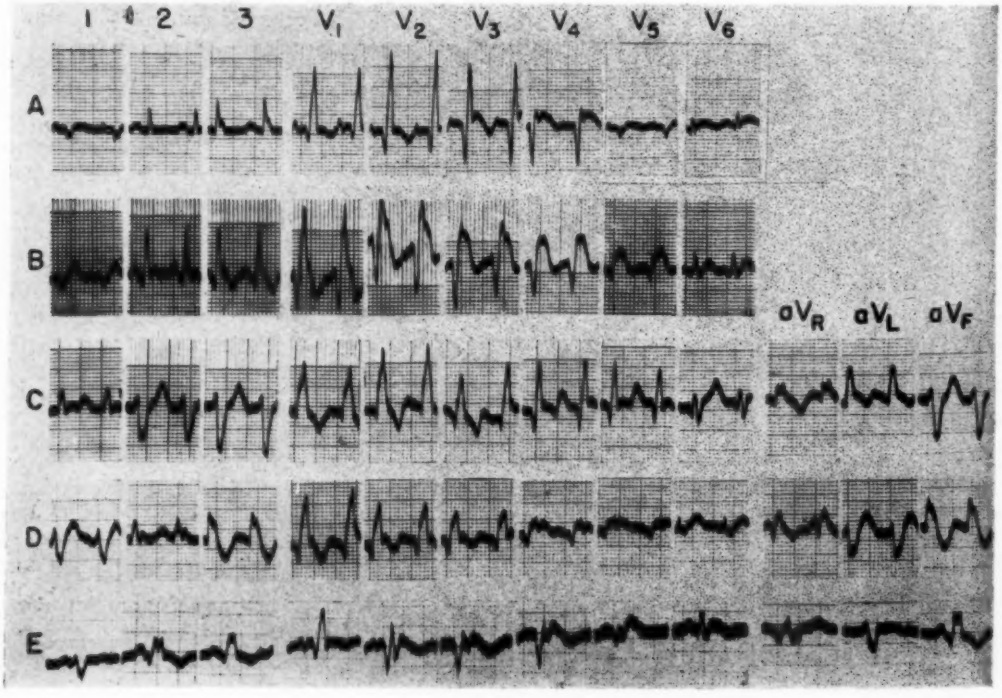


Fig. 3.—Right bundle branch block due to infarction of the interventricular septum. *A*, Case 70; *B*, Case 71; *C*, Case 72; *D*, Case 73; and *E*, Case 74.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the fourth hospital day is reproduced in Fig. 3, *A*. The QRS pattern in tracings on the second and fifth days was comparable to that in the illustration. The tall R wave and late intrinsicoid deflection in Leads $V_1$ through $V_3$ were diagnostic of right bundle branch block, and the abnormal initial Q waves in the same leads, together with the elevated RS-T segment and inverted T wave in Lead $V_3$, indicated that the right bundle branch block was due to a recent infarction of the septum. The QR complex of Lead $V_4$ was probably transitional. The QS deflection and elevated RS-T segment in Lead $V_5$ constituted evidence of recent infarction of the anterolateral wall of the left

ventricle, and the triphasic QRS complex and dome-like RS-T segment in Lead $V_6$ were ascribed to extension into the lateral wall. The standard leads showed right bundle branch block, but no definite evidence of infarction.

*Pathologic Findings.*—The heart weighed 375 grams and exhibited a recent infarct which involved the entire septum and adjacent anteroseptal wall but did not extend into the lateral or posterior wall of the left ventricle, nor into the right ventricle. The distribution throughout the entire length of the septum and anterior wall of the ventricle was similar to that in the third and fourth segments in Case 69 (Fig. 2), except that the lesion of the outer wall was transmural. It is noteworthy that there was no significant difference between the precordial leads in this case and those obtained on December 5 in Case 69, despite the fact that the infarct extended through the entire length of the septum in this case, yet spared the basal one-third of the septum in the previous case. There was good correlation between the infarction of the septum and the abnormal Q waves associated with the pattern of right bundle branch block in Leads $V_1$, $V_2$, and $V_3$. The predicted involvement of the lateral wall was not borne out at autopsy. In view of the rather marked clockwise rotation of the heart, it is probable that the potential variations of the infarcted anteroseptal wall of the left ventricle were transmitted into the axilla to account for the abnormal Q waves in Leads $V_5$ and $V_6$.

CASE 71.—A 53-year-old man was perfectly well until a fortnight prior to hospital admission, when he had a number of attacks of transient retrosternal oppression. He was admitted in shock after thirty hours of continuous retrosternal pain and died thirty-four hours later. No cardiac glycosides were given.

*Electrocardiographic Findings.*—An electrocardiogram obtained twenty-six hours after admission and following the administration of quinidine in doses of 0.2 Gm. hourly during the four preceding hours is reproduced in Fig. 3, *B*. This electrocardiogram, as well as a previous tracing taken on the first hospital day, showed auricular flutter with a 2:1 A-V ratio. The tall late R wave in Leads $V_1$ through $V_3$ was indicative of right bundle branch block and the marked elevation of the RS-T segment and the terminal inversion of the T wave in these leads were diagnostic of recent myocardial infarction. Close scrutiny of the tracing in Leads $V_1$ through $V_3$ revealed a sharp upstroke about 1.0 mm. in height at the onset of the QRS complex. The portion of this upstroke that corresponded in width with the remainder of the QRS complex was considered part of the ventricular complex rather than the flutter movement, despite the fact that measurements of the QRS interval that included this upstroke were 0.03 second longer than measurements made in the limb leads. Thus, the findings in right ventricular leads in this case differed from those in Cases 69 and 70 in that the QRS complex began with a minute upstroke rather than with a prominent Q wave. There was a questionable minute initial upstroke in transitional Lead $V_4$. However, left ventricular Lead $V_5$ revealed an abnormal Q wave, markedly elevated RS-T takeoff, and a monophasic upright T wave diagnostic of continuation of the septal infarct into the free anterior wall of the left ventricle. Lead $aV_F$ displayed a Q wave 0.03 second in duration and 3.0 mm. in depth followed by a 12.0 mm. R wave. Although the R wave was comparable in amplitude to that in Lead $V_1$, it was derived from the posterior wall of the left rather than the right ventricle, as shown by the fact that the intrinsicoid deflection was 0.04 second earlier in Lead $aV_F$ than in Lead $V_1$. The Q-R complex in Lead $aV_F$ was carried over into Leads II and III and was interpreted as evidence of extension of the infarct subendocardially into the posterior wall of the left ventricle.

*Pathologic Findings.*—The heart weighed 388 grams and revealed a recent, large transmural infarct which involved the entire anterior wall and the apical half of the lateral and posterior walls of the left ventricle. The infarct extended through the entire apical half of the septum and the anterior portion of the basal half, crossing over to involve the anterior wall of the right ventricle, as indicated by the area of avascularity in Fig. 4. The right bundle branch block was presumably due to the septal infarction. In the event that the initial upstroke in Leads $V_1$ through $V_3$ was a part of the QRS complex, it might have constituted an indirect effect of the destruction of the entire anterior portion of the septum and adjoining anteroseptal wall of the left ventricle. The early arrival of the activating impulse in this portion of the heart is normally responsible for the

initiation of negativity in the left ventricular cavity. The complete infarction of this area may have delayed the development of significant negative potentials in the left ventricular cavity in this case until the impulse reached and began to activate the intact basilar half of the lateral and posterior walls. In the meantime, weak, positive potentials referred to the right ventricular cavity from activation of the posterobasal remnant of the septum may have preponderated over the negligible negative potentials available for transmission from the left ventricular cavity through the infarcted septum to the right side of the precordium. Under these circumstances, a minute initial R wave might have been recorded in nearby right ventricular Leads $V_1$ through $V_2$ without a simultaneous counterpart in the remaining more distant leads, thereby accounting for the discrepancy in measurements of the QRS interval. It is noteworthy that a definite RSR′

**Fig. 4.—Roentgenogram of the injected heart in Case 71 with a large infarct of the anterior, lateral, and posterior walls of the left ventricle, the anterior wall of the right ventricle, and the septum, demarcated by its avascularity.**

complex, along with abnormal displacement of the RS-T segment, was registered in Leads $V_1$ through $V_2$ in Case 54, as a manifestation of a somewhat smaller, but comparably placed, infarct. The extension of the infarct into the anterior wall of the right ventricle caused no demonstrable modification in the QRS complex, but might have contributed to the marked elevation of the RS-T segment in Leads $V_1$ through $V_2$. The massive, transmural anterolateral infarction adequately explained the QRS-T pattern in Lead $V_5$, but should have led to an abnormal Q wave in Lead $V_6$, as well. The Q wave in Leads $aV_F$, III, and II was a manifestation of the posteroapical extension of the infarct.

CASE 72.—A 55-year-old man, who had a past history of angina pectoris, awakened with very severe retrosternal oppression, following which he lost consciousness. He was brought to

the hospital in shock with an arterial blood pressure of 82/60 and inaudible heart sounds. Death occurred nine hours later. No cardiac glycosides were given.

*Electrocardiographic Findings.*—An electrocardiogram obtained two hours after admission is reproduced in Fig. 3, *C*. The second tracing, taken five hours later, showed no significant change in the QRS complex. In Leads $V_1$ through $V_5$, there was an initial downstroke followed by a tall upstroke with late peak. The Q wave increased at the expense of the R wave as the electrode was moved from Position $V_1$ to $V_5$. The tall R wave and the postponement of onset of intrinsicoid deflection to 0.08 second in $V_1$ and $V_2$ were indicative of right bundle branch block, and the initial Q wave pointed to infarction of the septum. Because of a comparable Q-R pattern in Leads $V_3$ through $V_5$ and a simultaneous intrinsicoid deflection, beginning 0.08 second after the onset of the QRS complex, it was concluded that Leads $V_3$ through $V_5$ also were reflecting the potential variations of the epicardial surface of the right ventricle and the infarcted septum. The quadriphasic RSR'S' complex of Lead $V_6$ was considered transitional. The T waves were sharply inverted in Leads $V_1$, $V_2$, and $V_3$, diphasic in Leads $V_4$ and $V_5$, and upright in Lead $V_6$. This relationship suggested that the transition in T waves occurred in Leads $V_4$ and $V_5$, distinctly to the right of the transition in the QRS complex. Although the small Q wave and tall, slurred R wave recorded in Lead $aV_L$ might at first glance be regarded as left ventricular in origin, a comparison with the precordial leads showed that it corresponded much more closely with the pattern in right ventricular Leads $V_1$ through $V_3$ than with the findings in Lead $V_6$. This suggested that the potential variations of the right ventricle were referred to the left arm and those of the posterior aspect of the left ventricle, to the left leg. If this analysis of the precordial and Goldberger leads be correct, available tracings did not provide an adequate study of the anterior and anterolateral walls of the left ventricle. Thus, the only diagnosis justifiable from the electrocardiogram was that of a recent infarction of the interventricular septum. The standard leads showed a conduction defect, more suggestive of left than of right bundle branch block, but were not diagnostic of myocardial infarction.

*Pathologic Findings.*—The heart weighed 678 grams and exhibited left ventricular hypertrophy due to syphilitic aortic insufficiency. There was a very recent infarct involving the entire thickness of the interventricular septum, extending into the anterolateral wall of the left ventricle and across the septum into the anterior wall of the right ventricle. The position of the lesion was similar to that in Case 71 (Fig. 4), except that the posterior aspect of the left ventricle was spared. The right ventricle was markedly dilated, sufficiently so as to displace the transitional zone far to the left. It was believed that the Q-R pattern in Leads $V_1$ through $V_5$ was the result of the infarction of the interventricular septum, as recorded from the right ventricular side. Leads $V_7$ and $V_8$ would have been required for exploration of the left ventricle and for diagnosis of this portion of the infarct.

CASE 73.—A 38-year-old man gave a typical history of angina pectoris of three years' duration and of myocardial infarction, seven months previously. Within forty-eight hours of hospital admission he had two brief, but exceptionally severe, attacks of constrictive retrosternal pain. He was awakened by a third attack on the morning of admission and was brought to the hospital in shock. Death occurred sixteen hours later. No cardiac glycosides were given.

*Electrocardiographic Findings.*—An electrocardiogram obtained about four hours after the onset of the attack which necessitated hospitalization and fourteen hours before death is reproduced in Fig. 3, *D*. In Leads $V_1$ through $V_3$ there was a tall, slurred R wave and late intrinsicoid deflection, beginning 0.11 second after the onset of the QRS complex. These findings were diagnostic of right bundle branch block and the initial Q wave indicated underlying infarction of the interventricular septum. Leads $V_6$ and $aV_L$ displayed a small initial R wave, an early intrinsicoid deflection, and a broad, slurred S wave. These findings were typical of those registered over the normal left ventricle in right bundle branch block, except for the unusually low voltage of the R wave. Leads $V_4$ and $V_5$ showed an abnormal Q wave followed by a peculiar M-shaped summit, which could be resolved into a broad, slurred R wave and an elevated RS-T junction. The small, but precipitous, downstroke of the notch was identified as the intrinsicoid deflection. Since this downstroke was synchronous with the intrinsicoid deflection of Leads $V_1$ through $V_3$ and much

later than that in Lead $V_6$, it was concluded that Leads $V_4$ and $V_5$ were reflecting the potential variations of the region overlying or immediately to the right of the septum. Thus, the transitional zone was displaced to the left between Positions $V_5$ and $V_6$. The abbreviation of the intrinsicoid deflection consequent upon the marked elevation of the RS-T segment in Leads $V_4$ and $V_5$ suggested that the septal infarct reached the epicardial surface. The initial notch of the QRS complex in Lead $aV_F$ might have been a Q-wave equivalent, but was not sufficiently coarse for diagnostic inferences. The standard leads were typical of right bundle branch block, but revealed no definite evidence of recent infarction.

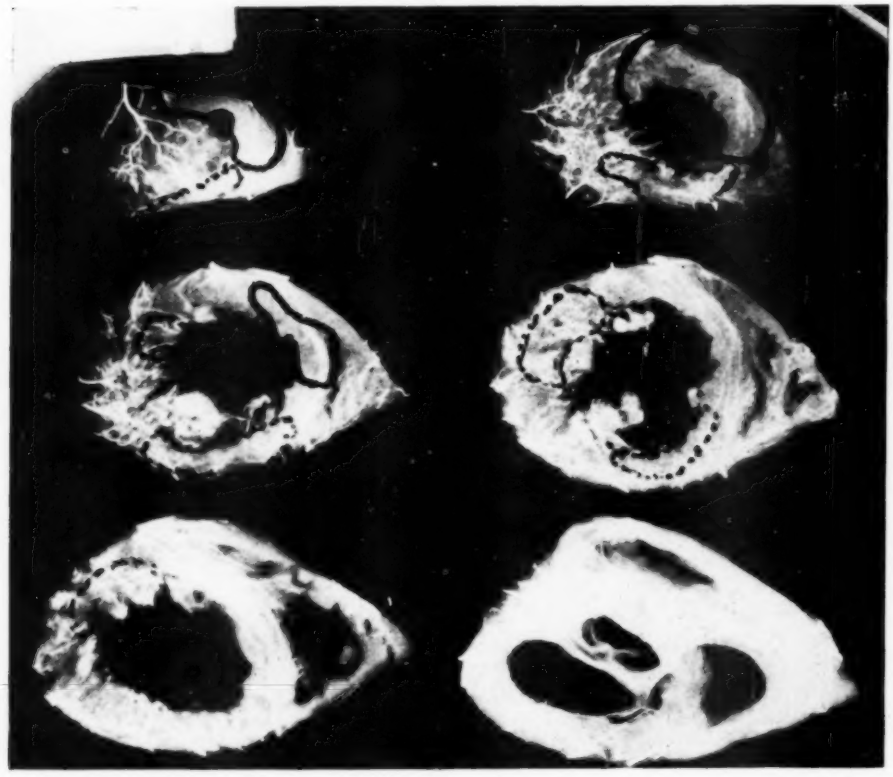

Fig. 5.—Roentgenogram of the injected heart in Case 73, showing old healed infarcts in broken outline and recent infarct of the anterior wall and septum in solid outline.

*Pathologic Findings.*—The heart weighed 465 grams and exhibited a recent infarct involving the entire septum and the adjoining anteroseptal wall of the left ventricle in the apical two segments and the anterior half of the septum and the adjoining subendocardial portion of the anteroseptal wall in the third segment, as demarcated by the solid lines of Fig. 5. It is noteworthy that a pattern consistent with right bundle branch block was apparently produced by an infarct confined to the apical half of the septum and that abnormal Q waves were recorded in right ventricular Leads $V_1$ through $V_3$, despite the fact that the basal half of the septum and the right ventricle were intact. Although abnormal Q waves in Leads $V_4$ and $V_5$ can usually be correlated with infarction of the anterolateral portion of the left apex, it was believed that this case constituted an exception. The fact that the time of onset of the intrinsicoid deflection of Leads $V_4$ and $V_5$ was similar to that of Leads $V_1$, $V_2$, and $V_3$ indicated that the Q waves of Leads $V_4$ and $V_5$, like those of Leads $V_1$ through $V_3$, were a manifestation of the septal rather than the left apical portion of the infarct. The involvement of the anteroseptal aspect of the left apex was missed

electrocardiographically because of the displacement of the transitional zone into the axilla. The low voltage of the initial R wave in Leads $V_6$ and $aV_L$ might have been secondary to infarction of the free wall of the left ventricle, but diagnostic signs of this lesion were absent. An old patchy infarct of the basal portion of the anterior wall (represented by the broken lines in Fig. 5) was also obscured by the right bundle branch block. A separate patchy infarct of the posterior wall, also indicated by broken lines, was not evident electrocardiographically, probably because of transmission of the potential variations of the right ventricle to the left leg.

CASE 74.—A 62-year-old man had had angina pectoris for three years. Attacks were brief in duration until ten days before hospital admission, when he was seized with severe retrosternal pain which lasted three days. He arose from bed for the first time on the day of admission and collapsed on the street with a recurrence of retrosternal constriction and dyspnea. He was brought to the hospital in shock and died five days later. No cardiac glycosides were given.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the second hospital day is reproduced in Fig. 3, *E*. Attention is directed to the similarity of this tracing to that obtained on December 1 in Case 69 (Fig. 1). The initial Q and tall R waves of Lead $V_1$, together with the delay in onset of the intrinsicoid deflection to 0.10 second, were indicative of right bundle branch block due to infarction of the interventricular septum. The slight elevation of the RS-T segment in Lead $V_1$ suggested that the septal lesion was of recent origin. Because of the broad S wave in all leads to the left of Lead $V_1$, it was concluded that the transitional zone was near the left sternal border and that Leads $V_2$ through $V_6$ reflected the potential variations of the anterolateral wall of the left ventricle. The abnormal Q wave and the upward displacement of the RS-T junction in Leads $V_2$ through $V_6$ were construed as evidence of continuation of the recent septal infarct into the anteroseptal and anterolateral aspects of the left apex. The small R and broad S waves of Lead $aV_L$ represented the pattern recorded over the normal left ventricle in right bundle branch block and were probably transmitted from an uninfarcted basal portion of the lateral wall. From a first glance at Leads $aV_F$, II, and III, one might be tempted to attribute the abnormal Q wave in these leads to coexistent posterior infarction. However, the late intrinsicoid deflection in Lead $aV_F$ indicated that this lead, like Lead $V_1$, reflected the potential variations of the right ventricle. Thus, the abnormal Q wave in Leads $aV_F$, II, and III, like that in Lead $V_1$, could have been produced by the septal infarction.

*Pathologic Findings.*—The heart weighed 430 grams and exhibited a recent infarct of the interventricular septum which extended into the anterolateral and posteroapical aspects of the left ventricle in a manner almost identical with that in Case 69 (Fig. 2). The right ventricle was uninvolved. The infarct of the anterior wall of the left ventricle was confined to the subendocardial one-half except in the apical segment, where it was transmural, and thus was well correlated with the findings in Leads $V_2$ through $V_6$. The entire interventricular septum was infarcted, not only in the first four segments, as in Fig. 2, but also in the basal segment, as well. This accounted for the abnormal QRS-T pattern in Leads $V_1$ and $V_2$. In addition to the extension of the acute infarct into the posterior aspect of the apical segment, there was an old, completely healed, patchy infarct occupying the basal three-fifths of the posterior wall of the left ventricle. Nevertheless, the abnormal Q wave recorded in Leads $aV_F$, II, and III was believed referable to the infarction of the septum rather than to the lesion of the posterior wall, for reasons already given.

CASE 75.—A 58-year-old man gave a typical history of angina pectoris, beginning two months before hospital admission, and was hospitalized in his first prolonged attack of retrosternal constriction. Despite strict confinement to bed, there were repeated attacks of retrosternal pain, usually relieved by nitrites and papaverine. Systolic and diastolic pressures were consistently subnormal. The patient suddenly died during a meal on the thirty-third day. No cardiac glycosides were given.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the twelfth hospital day is reproduced in Fig. 6, *A*. Right bundle branch block was established by the tall, coarsely slurred R wave and the 0.10 second interval preceding the intrinsicoid deflection in Lead $V_1$. A diagnosis of infarction of the septum was made from the presence of a Q wave instead of the expected initial

R wave in Lead $V_1$. The early attainment of the peak of the R wave (0.03 second after the onset of the QRS complex) and the broad, slurred S wave in Leads $V_4$ through $V_6$ represented the typical findings obtained through precordial leads over the normal left ventricle in cases of right bundle branch block. In Leads $V_2$ and $V_3$ the intrinsicoid deflection began after an interval of 0.07 and 0.06 second, respectively, and was followed by a definite S wave, which was not as broad as that in leads farther to the left. The pattern in Leads $V_2$ and $V_3$ was thus transitional between that of Leads $V_1$ and $V_4$, indicating that the electrode was in close proximity to the interventricular septum. The abnormal Q wave in Leads $V_2$ and $V_3$ constituted further evidence of septal infarction. The significant difference between the precordial leads in this case and in the majority of the six preceding cases lay in the absence of Q waves from leads over the anterolateral aspect of the left ventricle (Leads $V_4$ through $V_6$). This was interpreted as evidence that this septal infarct did not extend into the anterolateral aspect of the left apex. The resemblance of the QRS complex in Lead $aV_F$ to that in Lead $V_6$ signified that the potential variations of the left ventricle were transmitted to the left leg. The small W-shaped QRS complex of Lead $aV_L$ was regarded as a transitional complex, transmitted from the neighborhood of the interventricular septum, due to semivertical position of the heart. The QRS complexes in three other tracings taken during hospitalization were essentially the same as in the electrocardiogram reproduced in Fig. 6, *A*. Over this period the T waves in Leads $V_1$ through $V_3$ showed gradually increasing depth associated with the organization of a recent infarct. The standard leads showed right bundle branch block, but were not diagnostic of infarction, either in single or serial tracings.

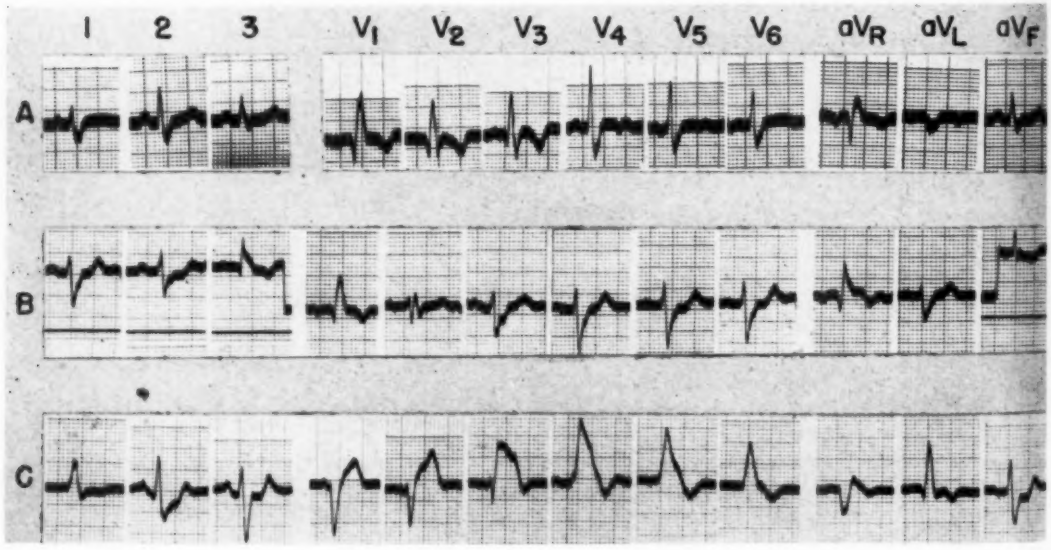


Fig. 6.—Primary septal infarction. *A*, Case 75; *B*, Case 76; *C*, Case 77.

*Pathologic Findings.*—The heart weighed 563 grams and exhibited left ventricular hypertrophy and right ventricular dilatation. An organizing infarct occupied the greater portion of the interventricular septum and extended into the anteroseptal wall of the mid-portion of the left ventricle, as represented by the solid lines in Fig. 7. On gross inspection the infarct appeared to be limited to the left ventricular half of the septum, but on microscopic examination it extended in patchy fashion to the endocardium of the right side of the septum. The broken lines projecting posteriorly represented an older area of patchy subendocardial infarction, which was continuous in the septum with the more recent infarction. Despite the fact that the infarct was much denser in the left then in the right half of the septum, the conduction defect involved the right rather than the left bundle branch. The localization of the abnormal Q waves to right

ventricular Lead $V_1$ and to transitional zonal Leads $V_2$ and $V_3$ conformed closely with the limitation of the infarct to the septum and subendocardial portion of the adjacent anteroseptal wall. The absence of infarction of the anterolateral wall in the apical two segments could be correlated with the normal initial phase of the QRS complex in Leads $V_4$ through $V_6$ and confirmed the ante-mortem interpretation of Lead $aV_L$. The older infarct of the subendocardial portion of the posterobasal wall was not demonstrable by electrocardiogram.

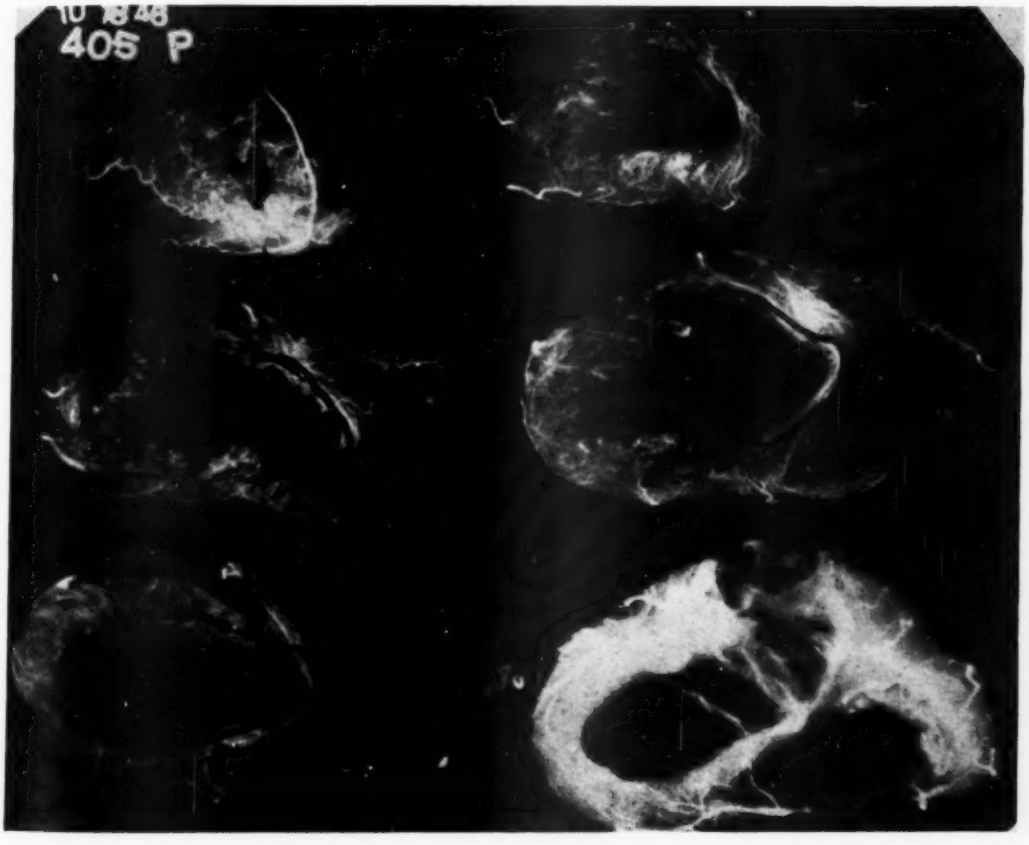


Fig. 7.—Roentgenogram of the injected heart in Case 75, showing recent septal infarct in solid lines and old, healed posterior infarct in broken lines.

CASE 76.—A 77-year-old hypertensive woman had been free of cardiovascular symptoms until four days before admission to the hospital, when she was suddenly seized with severe epigastric pain, accompanied by dyspnea and extreme prostration. She was admitted in severe congestive heart failure and circulatory collapse and died four hours later. No cardiac glycosides were given.

*Electrocardiographic Findings.*—An electrocardiogram obtained one hour after admission is reproduced in Fig. 6, *B*. The prominent slurred R wave in Lead $V_1$ and the interval of 0.09 second preceding the onset of the intrinsicoid deflection in this lead were indicative of right bundle branch block. The early onset of the intrinsicoid deflection in Leads $V_3$ through $V_6$ and the subsequent broad, slurred S wave represented the typical pattern registered through precordial leads over the left ventricle in cases of right bundle branch block. Because of the normal initial phase of the QRS complex in these leads, it was concluded that the anterior wall of the left ventricle was

not infarcted. A diagnosis of septal infarction was strongly suggested by the initial Q wave in Lead $V_1$, but was not supported by the findings in Lead $V_2$. The latter was apparently a transitional lead recorded from a point in the vicinity of the septum and showed an initial R wave rather than the Q wave to be expected if the septum were infarcted. A diagnosis of infarction of the muscle immediately beneath the endocardium of the right side of the septum was suggested by the elevation of the RS-T junction in Lead $aV_R$. Because of the transmission of potential variations of the endocardial surface of the right side of the septum to the right ventricular cavity and thence to the right arm, injury to the muscle immediately beneath this portion of the endocardium might cause displacement of the RS-T segment in Lead $aV_R$ analogous to that produced in Lead $aV_L$ by injury to the subepicardial muscle of the lateral wall of the left ventricle. However, caution was also needed in making diagnostic inferences from the high RS-T take-off in Lead $aV_R$, since we have observed greater elevation in this lead in a case of right bundle branch block associated with hyperpotassemia, but without pathologic evidence of myocardial infarction. Thus, in the ante-mortem interpretation, the tracing was considered strongly suggestive, but not pathognomonic, of infarction limited to the septum. The small Q wave in Lead III was of no significance because inspection of the Goldberger leads showed that it was derived from initial positivity of the left arm rather than initial negativity of the left leg.

*Pathologic Findings.*—The heart weighed 590 grams and revealed a recent comma-shaped infarct, extending through the septum in the second, third, and fourth segments in a fashion almost identical with the lesion in the second and third segments in Case 83 (Fig. 15). This infarct continued for a distance of 1.0 cm. into the subendocardial half of the adjoining anterior wall of the left ventricle. The remainder of the free wall of the left ventricle and the entire outer wall of the right ventricle were intact. The disproportion between the relatively small infarct at autopsy and the severe congestive failure and circulatory collapse during life is noteworthy. The Bernheim syndrome could not be demonstrated at autopsy and no other cause for death was found. The initial Q wave of Lead $V_1$ was regarded as a manifestation of the septal infarct and the initial R wave in transitional Lead $V_2$ was best explained by the assumption that the potential variations of the electrode were dominated by those of the uninfarcted anterior wall of the left ventricle, just to the left of the septum. The normal initial phase of the QRS complex in Leads $V_3$ through $V_6$ was well correlated with the absence of pathologic evidence of infarction of the anterolateral wall of the left ventricle. The elevation of the RS-T segment in Lead $aV_R$ was probably due to the septal infarction, and the slight depression of the RS-T segment in Leads $V_4$ and $V_5$ may have been a reciprocal effect.

CASE 77.—A 71-year-old man had been perfectly well until the morning of admission to the hospital, when he was suddenly seized with severe oppressive pain in the precordium, radiating into the left shoulder and arm, accompanied by marked dyspnea and followed by syncope. He was brought to the hospital in profound collapse with unobtainable blood pressure and died twelve hours later.

*Electrocardiographic Findings.*—An electrocardiogram taken four hours after the onset of pain and eleven hours before death is reproduced in Fig. 6, *C*. The pacemaker shifted between the sinus and A-V node. The striking feature of the precordial leads was the extreme elevation of the RS-T segment in Leads $V_3$ and $V_4$ and the less marked, but definitely abnormal, elevation in Leads $V_1$, $V_2$, and $V_5$. The displacement of the RS-T segment in Leads $V_3$ and $V_4$ was greater than is observed in pericarditis and was considered diagnostic of very recent anterior infarction. The presence of an initial R wave in all precordial leads was an unusual finding, but might be associated with acute anterior infarction under the following circumstances: (a) Limitation of the infarct to the subepicardial layer of the anterior wall, or (b) presence of a very patchy lesion, which spared the major portion of the myocardium. (Neither of these possibilities could scarcely have explained the profound shock and early death.) (c) Complicating left bundle branch block, or (d) infarction of subendocardial layer of the left side of the septum, which destroyed the Purkinje network rather than the left bundle branch. Either left bundle branch block or destruction of the left side of the septum should reverse the vector associated with septal activation, with consequent reference of negative potentials to the right ventricular cavity and positive potentials

to the left ventricular cavity. Both of these possibilities warranted consideration, in view of the contour of the QRS complex in Leads $V_4$, $V_5$, and $V_6$ and the QRS interval of 0.13 second in these leads. However, the S wave in Leads $V_1$, $V_2$, and $V_3$ was not as broad as would be expected under these circumstances and the distinct Q wave preceding the tall R wave of Lead $aV_L$ was difficult to reconcile with either alternative. (e) A very early transmural infarct, too brief in duration for obliteration of the response to the activating impulse, was in keeping with the short interval between the onset of the pain and the recording of the electrocardiogram and seemed the best explanation for the abnormally prolonged R wave in Leads $V_4$ through $V_6$, and the broad Q wave in Lead $aV_L$. The depression of the RS-T segment in Lead $aV_F$ was considered reciprocal to the elevation in leads over the anterior wall of the left ventricle. This depression was carried over into Leads II and III. The pattern in the standard leads was abnormal, but was not characteristic of an infarction.


Fig. 8.—Roentgenogram of the injected heart in Case 77.

*Pathologic Findings.*—The heart weighed 506 grams and exhibited a brownish discoloration of the left side of the anterior two-thirds of the septum and the adjacent anterolateral wall of the mid-portion of the left ventricle, as outlined in Fig. 8. Multiple microscopic blocks revealed a very recent infarct extending through the entire thickness of the anterior wall and septum in the area outlined. The subepicardial portion of the acute anterolateral infarct presumably accounted for the marked elevation of the RS-T segment. The septal lesion did not extend high enough to have reached the left bundle branch. Since the entire thickness of the septum was infarcted, the hypothesis of an initial R wave in the precordial leads produced by activation of the septum

from right to left did not seem very likely. On the whole, the recording of an initial upright, rather than a downward, deflection in Leads $V_4$, $V_5$, and $V_6$ was best explained by the supposition that the lesion was too early for complete obliteration of the response to the activating impulse.

CASE 78.—A 60-year-old man gave a four-month history of repeated attacks of typical anginal pain. These attacks came at rest, as well as on exertion, and generally lasted from five to thirty minutes until Jan. 21, 1947, when a prolonged attack of exceptionally severe pain occurred which necessitated hospitalization. Physical examination revealed syphilitic aortic insufficiency and severe congestive heart failure, necessitating maintenance on digitalis throughout hospitalization. On the morning of January 29 he was found in shock with a rapid, totally irregular ventricular rhythm. Quinidine was instituted and continued in a dose of 0.25 Gm. every four hours for the remainder of his hospital stay. A pericardial friction rub was heard for the first time on January 30. Death occurred on Feb. 2, 1947.

*Electrocardiographic Findings.*—Electrocardiograms selected from a series obtained during his thirteen days of hospital stay are reproduced in Fig. 9. On January 24 sinus rhythm was present. On January 30 there was an auricular tachycardia with auricular rate of 230, usually with variable ventricular response, but with intermittent 2:1 ratio, as seen in Lead $V_2$. On February 1 there was a wandering pacemaker between sinus and A-V nodes, well brought out in Lead II. The disturbance in auricular rhythm which developed on January 29 raised the question of extension of an infarct into the atria. The pattern of the QRS complex in the standard leads was fairly typical of left bundle branch block and was quite constant throughout, except for lengthening in QRS interval from an original measurement of 0.14 to 0.16 second. Although minor changes were observed in the T waves in the standard leads, there were no findings in these leads which were considered diagnostic of recent infarction. On the other hand, the precordial leads showed definite signs of recent infarction and furnished evidence of a different type of conduction defect from that postulated from the standard leads. In Lead $V_6$ there was an initial R wave, which reached its peak within 0.04 second, and a subsequent broad, slurred S wave, strongly suggestive of right bundle branch block. At first glance, the QRS complex of Leads $V_1$ through $V_3$ appeared to consist solely of a downward deflection; however, the time interval, as measured from the beginning of the QRS complex in Leads $V_1$ through $V_3$ to the end of the steep upstroke, was only 0.10 second, whereas the duration of the QRS complex, as measured in both the standard leads and Lead $V_6$, was 0.14 second. More careful scrutiny of Leads $V_1$ through $V_3$ revealed an elevated, slurred plateau which, from measurements, was considered part of the R wave, the RS-T junction being marked by a slight dip. The findings in Leads $V_1$ through $V_3$ were transmitted from the right, rather than the left, side of the heart, as evidenced by the diphasic P waves, indicating proximity of the electrode to the right atrium and by the later attainment of the peak of the R wave in these leads than in Lead $V_6$. Thus, the late, broad, slurred R wave detected by careful scrutiny of Leads $V_1$ through $V_3$ established the presence of right bundle branch block, and the initial Q wave in these leads was indicative of infarction of the interventricular septum. The pattern in Leads $V_4$ and $V_5$ differed significantly both from that in Leads $V_1$ through $V_3$ and from that in Lead $V_6$. Although the transitional zone in right bundle branch block may be displaced as far to the left as $V_4$ or $V_5$, the late R wave derived from the delayed activation of the outer wall of the right ventricle attains its maximum in Lead $V_1$ or $V_2$ and diminishes as the electrode is moved farther to the left. Thus, it was concluded that the late R wave in Leads $V_4$ and $V_5$ was of left, rather than right, ventricular origin. The normal P-R interval indicated that left, as well as right, bundle branch block could not be present, and the 0.04 second interval between the onset of the QRS complex and the beginning of the intrinsicoid deflection in Lead $V_6$ also excluded complete left bundle branch block. The initial Q wave and the subsequent prolonged slurred ascending limb of the R wave and postponement of the intrinsicoid deflection to 0.08 second in Leads $V_4$ and $V_5$ indicated that the conduction defect was in the anterolateral aspect of the outer wall of the left ventricle. From the Q-R pattern in Leads $V_4$ and $V_5$, together with the elevated RS-T junction and cove-shaped inversion of the T wave in Lead $V_4$, a diagnosis was made of anterolateral infarction, dense in the subendocardial layer and patchy in the mid-zone and subepicardial layer. The late R wave in Leads $V_1$ and $V_2$, due to right bundle branch block, increased greatly in amplitude in the tracing of February 1, and the transitional zone shifted to

the left. A Q wave appeared in Leads $V_6$ and $aV_L$, which, together with the elevation of the RS-T junction in Leads $V_4$ through $V_6$, suggested extension of the infarct farther into the lateral wall of the left ventricle.

*Pathologic Findings.*—The heart weighed 719 grams, as a result of left ventricular hypertrophy from syphilitic aortic insufficiency. There was a large horseshoe-shaped infarct, occupying the subendocardial half of the anterior and lateral walls of the left ventricle and the interventricular

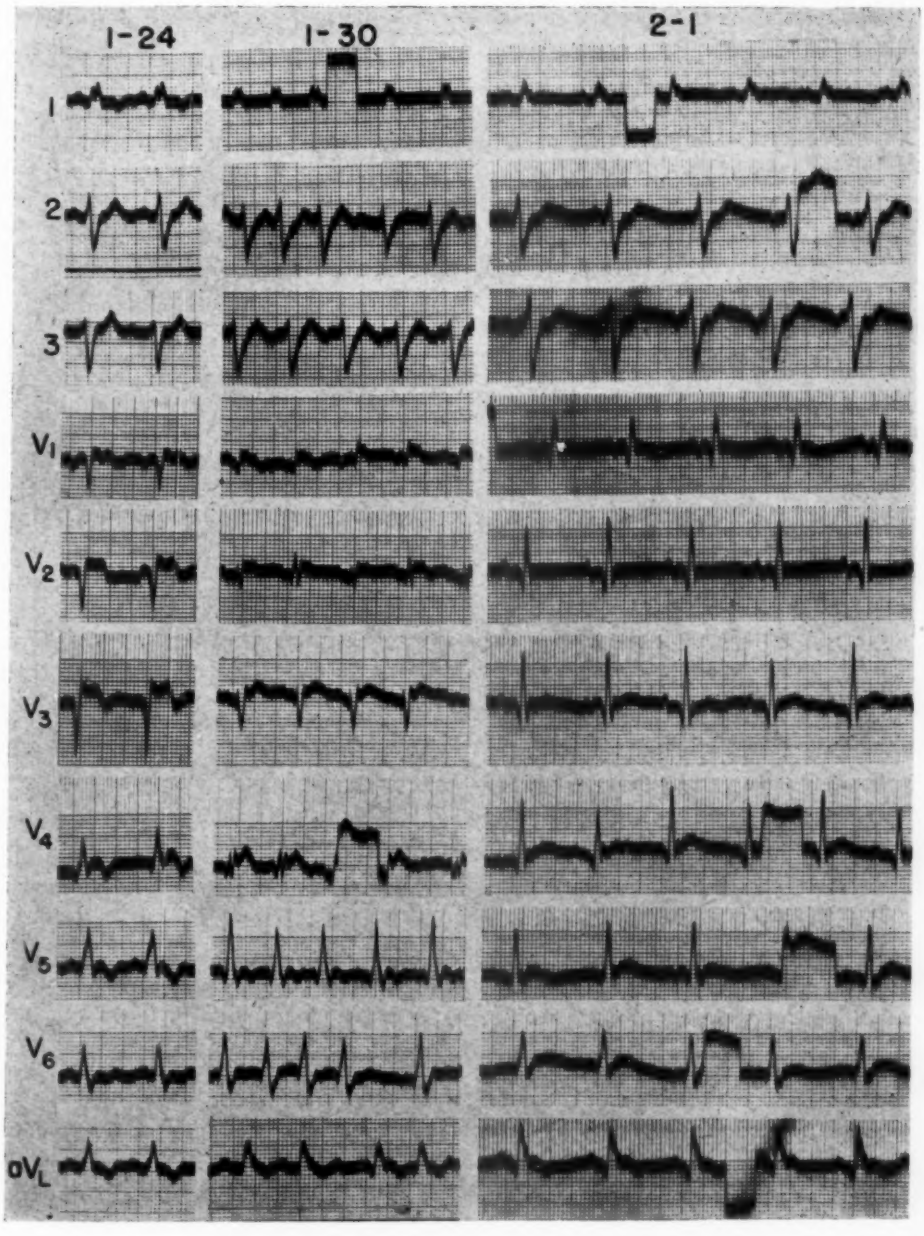


Fig. 9.—Serial electrocardiograms in Case 78.

septum in all segments. The area of involvement in each of the six segments was similar to the avascular portion of the second segment of Fig. 11, which represents the roentgenogram of the heart in Case 79. The outer wall of the right ventricle was intact. The infarction of the interventricular septum was deemed responsible for the right bundle branch block and the abnormal Q-wave pattern in Leads $V_1$ and $V_2$ and probably in Lead $V_3$. Sections through the anterior wall showed patchy fibrosis, which was presumably a remnant of the numerous episodes of coronary insufficiency and, in addition, revealed an organizing infarct, which was fairly dense in the subendocardial half, but very patchy in the subepicardial half. The age and distribution of the organizing infarct satisfactorily accounted for the abnormal initial Q wave and delayed peak of the R wave in Leads $V_4$ and $V_5$. Sections from the lateral wall showed a similar patchy fibrosis and, in addition, a fairly dense subendocardial infarct of two to four days' duration. This lesion could be correlated with the serial changes in the QRS-T pattern in Leads $V_5$, $V_6$, and $aV_L$. An organizing mural thrombus was found in the right auricle, but unfortunately no microscopic sections were taken to settle the question of atrial infarction.

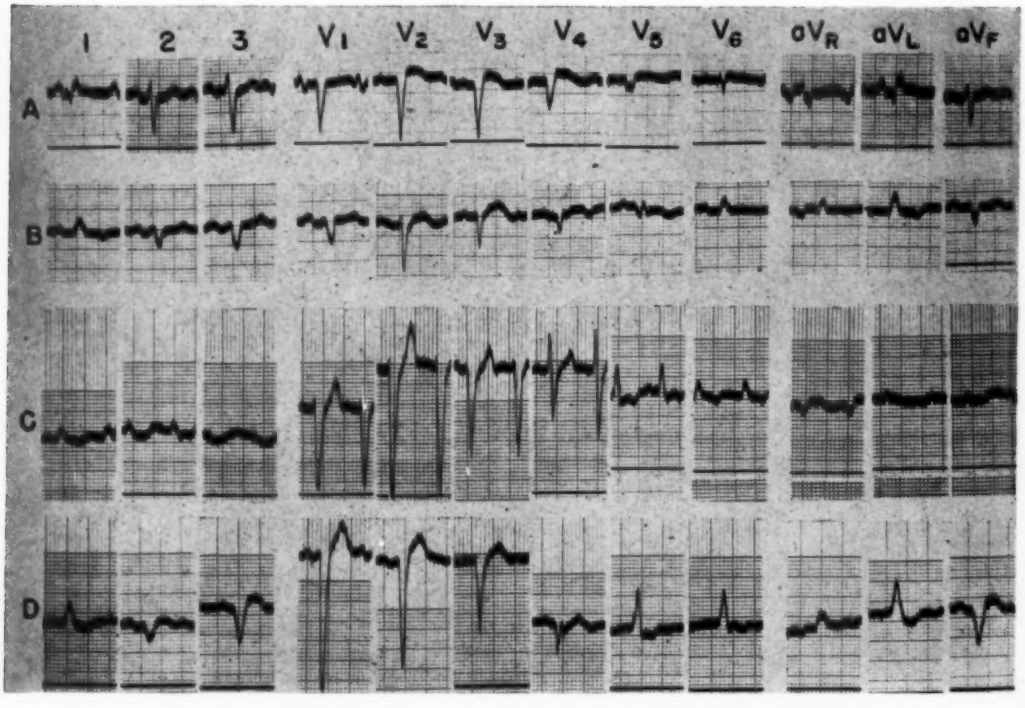


Fig. 10.—Infarction of the septum and anterior wall of the left ventricle.
*A*, Case 79; *B*, Case 80; *C*, Case 81; *D*, Case 82.

CASE 79.—A 71-year-old man was admitted to the hospital moribund, one and one-half hours after the sudden onset of extreme orthopnea, not accompanied by chest pain. Past history was negative, except for exertional dyspnea of six weeks' duration. He made a dramatic response to therapy, which included 1.6 mg. of Cedilanid intravenously, and was quite comfortable until the ninth day, when there was a recurrence of dyspnea, accompanied by shock. He rallied following redigitalization, but died suddenly on the twelfth day.

*Electrocardiographic Findings.*—An electrocardiogram obtained twenty-three hours after admission is reproduced in Fig. 10, *A*. The finding of a small, but definite, initial R wave in Lead $V_1$, a QS complex in Leads $V_2$ through $V_4$, a W-shaped QRS complex of low voltage in Leads $V_5$

and $V_6$, and an abnormal QR complex in Lead $aV_L$ was diagnostic of a large transmural infarct of the anterior and anterolateral walls of the left ventricle, becoming subendocardial farther in the lateral wall. The contour of the RS-T segments and T waves in Leads $V_2$ through $V_4$ was suggestive of recent infarction. The QRS interval of 0.12 second was indicative of a conduction defect and the abnormal Q wave in precordial leads over the left ventricle and in Lead $aV_L$, together with the notched late R wave of Lead $aV_L$, constituted strong evidence that the conduction defect was located in the free wall of the left ventricle. If left bundle branch block had been responsible for the QRS prolongation, an initial R wave would have been expected in left ventricular leads, because of early positivity of the left ventricular cavity, resulting from activation of the septum from right to left. The registration of an abnormal Q wave in leads over an anterolateral infarct is possible in the presence of left bundle branch block, if the entire septum, or the major portion of it, is unresponsive because of infarction. Under these circumstances, the left ventricular cavity might become initially negative, because of potentials derived from the activation of the outer wall of the right ventricle and transmitted through the inert septum, and would subsequently show increasing negativity as the impulse reached and activated uninfarcted portions of the outer wall of the left ventricle. The combination of complete infarction of the septum and bundle branch block was considered very remote in this case, because the QRS interval should have been considerably greater than 0.12 second under those conditions. Standard Lead I was also diagnostic of anterolateral infarction.

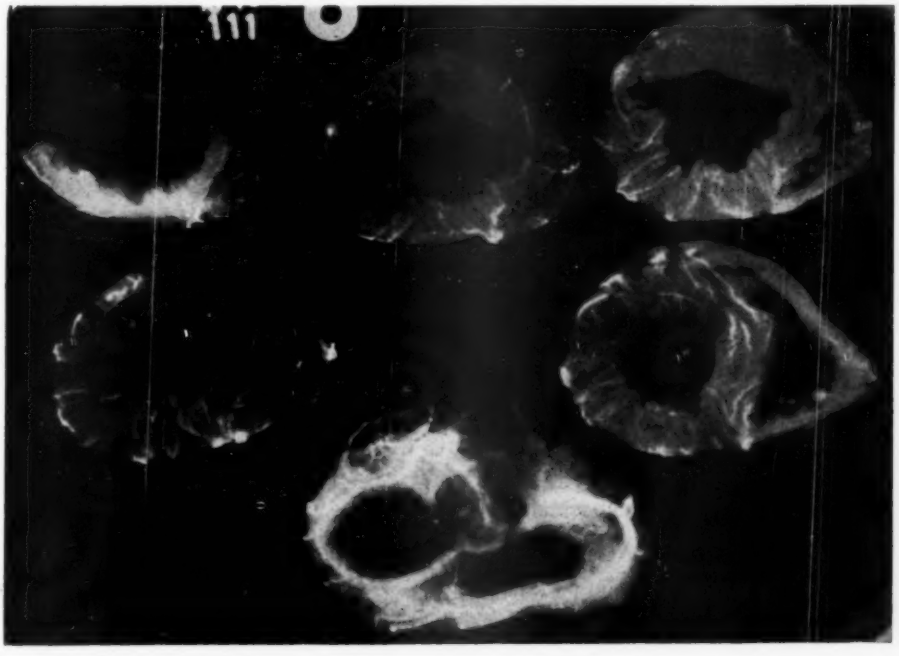

**Fig. 11.—Roentgenogram of the injected heart in Case 79 with large anterolateral and septal infarct, demarcated by its avascularity.**

*Pathologic Findings.*—The heart weighed 598 grams and exhibited a large transmural infarct, represented by the avascular areas in Fig. 11. In the apical segment, this lesion occupied the circumference of the left ventricle; in the second and third segments it involved the entire anterior wall and the anterior one-half to one-third of the lateral and septal walls and extended across the latter to include a narrow strip of the adjoining right ventricle; in the fourth segment it was confined to the anteroseptal aspect of the left ventricle. The anterior wall of the left ventricle

in the apical three segments was actually only 5.0 mm. in thickness. The remainder of the roentgenographic shadow consisted of mural thrombus, which completely filled an aneurysmal sac created by the herniation of the anterior wall. Microscopic examination revealed an old, patchy anteroseptal infarct estimated to be about two months in duration with a superimposed organizing infarct of the anterior, lateral, and septal walls estimated to be about two weeks in duration. The conduction defect was probably located in the incompletely infarcted lateral wall rather than the septum, because of the moderate prolongation of the QRS complex, the abnormal Q-wave pattern in all leads facing the anterolateral wall, and the absence of infarction of the basal half of the septum at autopsy. The septal and right ventricular portions of the infarct were not evident electrocardiographically. The possibility that the extension into the septum and anterior wall of the right ventricle might have occurred during the attack on the ninth hospital day was not supported by the pathological evidence. There was good correlation between the findings in Leads $V_2$ through $V_6$ and $aV_L$ and the infarction of the anterolateral wall found at autopsy. The extension into the posterior aspect of the apical segment was not diagnosed ante mortem, probably because of horizontal position of the heart.

CASE 80.—A 79-year-old woman entered the hospital because of a fractured femur, which was treated by surgical reduction. Three days postoperatively she complained of a sudden sense of impending death, which was not accompanied by actual pain. Congestive failure ensued and persisted until death twenty days later.

*Electrocardiographic Findings.*—An electrocardiogram obtained nine days after the onset of the sense of impending death and following the administration of 0.6 Gm. of digitalis is reproduced in Fig. 10, *B*. A diagnosis of recent anterolateral infarction was made from the abnormally reduced initial R wave and dome-like elevation of the RS-T segment in Lead $V_3$, together with the QR complexes and cove inversion of the T waves in Leads $V_4$ and $V_5$. Several other tracings taken from four to eighteen days after the onset of the present illness showed a comparable QRS pattern, together with the usual RST-T evolution found in recent organizing anterolateral infarction. The question arose as to the site of the conduction defect responsible for prolongation of the QRS interval to 0.12 second. Left bundle branch block was suggested by the broadened, slurred initial R wave recorded in Leads $V_6$, $aV_L$, and I. To reconcile the association of left bundle branch block with the presence of Q waves in left ventricular Leads $V_4$ and $V_5$, it was necessary to postulate that the anterior infarct had involved the entire septum or the major portion of it. Destruction of the septum would be expected to eliminate the customary initial positivity of the left ventricular cavity resulting from aberrant septal activation in left bundle branch block, thereby making possible the registration of a Q wave in leads overlying an anterolateral infarct, as discussed in connection with Case 79. However, the circuitous route of left ventricular activation necessitated under these conditions should have caused greater prolongation of the QRS interval. For this reason, serious consideration was given to an alternative explanation for the QRS pattern in Leads $V_6$, $aV_L$, and I, namely, a very patchy transmural infarction of the lateral wall. Such a lesion might cause sufficient delay in the passage of the impulse through the lateral wall to cause prolongation of the QRS complex to 0.12 second and sufficient reduction in electromotive force to account for the low voltage of the R wave. Because of the similarity of the slurred R wave recorded in Lead $aV_R$ to that in $aV_L$, it was probable that the heart was rotated backward on its transverse axis, thereby facilitating transmission of the potential variations of the posterobasal aspect of the left ventricle to both upper extremities.

*Pathologic Findings.*—The heart weighed 567 grams and showed a very large organizing infarct, involving the entire apical two-thirds of the septum and the anterior part of the basal one-third, along with most of the anterior wall of the left ventricle, the apical one-half of the lateral wall, and the apical one-third of the posterior wall. The distribution of the lesion in the left ventricle was almost identical with that in Case 71 (Fig. 4), but the right ventricle was spared in the present case. The infarct involved the entire thickness of the anterior and anterolateral walls, but was patchy in distribution, which apparently accounted for the small late R wave of Leads $V_4$ and $V_5$ and the reduced initial R wave of Lead $V_3$. The patchy infarct of the lateral wall of the left ventricle could have accounted for both the low voltage and slurring of the R wave

in Leads $V_6$ and $aV_L$ and seemed a better explanation for the 0.12 second interval of the QRS complex than left bundle branch block complicated by septal infarction. However, the latter alternative could not be definitely excluded, since it is possible that activation of the small intact remnant of the septum might have occurred from right to left (as a result of left bundle branch block) without producing positive potentials of sufficient magnitude for the registration of an initial R wave in left ventricular leads.

CASE 81.—A 74-year-old man, who had been under treatment elsewhere for peptic ulcer, was suddenly stricken with severe midepigastric pain, accompanied by shortness of breath and followed by delirium. He was admitted to the hospital in circulatory collapse and died on the ninth hospital day.

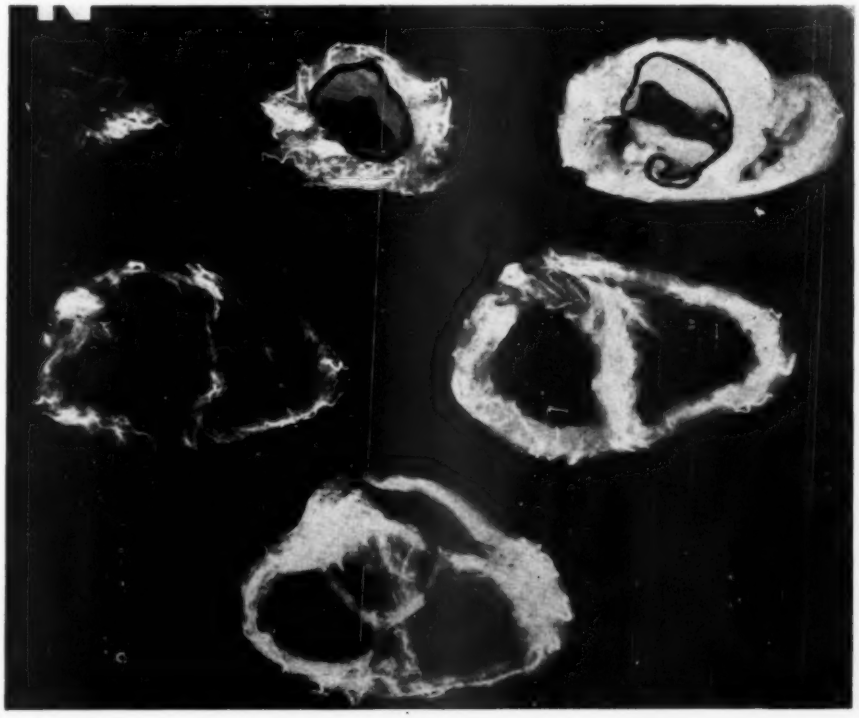

**Fig. 12.—Roentgenogram of the injected heart in Case 81, showing position of the infarct in the septum and the subendocardial portion of the anterior and posterior walls.**

*Electrocardiographic Findings.*—An electrocardiogram obtained five days after the onset of sudden epigastric pain and before the administration of digitalis is reproduced in Fig. 10, *C*. The initial phase of the QRS complex was upright in all precordial leads, in Lead $aV_L$, and in Lead $aV_F$. The R wave was of borderline amplitude in Lead $V_5$ and was of abnormally low voltage in left ventricular Lead $V_6$, $aV_L$, and $aV_F$ and in the standard leads. However, a broad, deep S wave of left ventricular origin was recorded in Leads $V_1$ and $V_2$. This suggested that the low voltage in axillary and limb leads may have been due to an extracardiac cause, such as emphysema. The QRS interval, as measured in Leads $V_1$, $V_2$, and $V_3$, was 0.12 second. The broad, slurred R wave in left ventricular leads and widened S wave in right ventricular leads indicated that the conduction defect was situated in the left ventricle and the presence of an initial upright deflection in all leads over the left ventricle pointed to left bundle branch block. Attention is directed to the fact that the initial R wave in Leads $V_1$ and $V_2$ measured 2.0 to 3.0 mm. and fell off to 1.0 mm. in

Lead $V_3$. This was abnormal and raised the question of patchy anteroseptal infarction, but, in the ante-mortem interpretation, was not considered sufficiently decisive to permit a definite diagnosis. The upright T waves in Leads $V_1$ through $V_4$ and the depressed RS-T junction and inverted T waves of Leads $V_5$ and $V_6$ were compatible with those encountered in left bundle branch block or left ventricular hypertrophy and were not considered diagnostic of infarction. The tall, sharply peaked T wave in Lead $V_2$ was somewhat suggestive of hyperpotassemia, which may have been present, in view of the fact that the blood urea reached 272 mg. per cent. Unfortunately, no subsequent electrocardiograms were obtained for comparative purposes during the last four days of his life.

*Pathologic Findings.*—The heart weighed 360 grams and exhibited a dense infarct, involving the subendocardial half of the anteroseptal wall, extending through the left side of the septum to the subendocardial one-third of the posteroseptal wall, as outlined in Fig. 12. The infarct was recent in origin, but was believed to have been present at the time the electrocardiogram was made and was presumably responsible for the epigastric pain at the onset of his present illness, since no other cause was found. The paucity of diagnostic electrocardiographic signs is noteworthy. Q waves would have been expected in Leads $V_3$ and $V_4$, in view of the dense infarct of the subendocardial half of the anteroseptal wall, but not in Leads $V_5$ and $V_6$, since the infarct did not extend appreciably into the lateral wall. A Q wave would also have been expected in Lead $aV_F$, which reflected the potential variations of the subendocardially infarcted posterior wall of the left ventricle. The presence of an initial R wave in Leads $V_3$, $V_4$, and $aV_F$ was due most likely to reversal in septal activation to a direction from right to left. This might have resulted from coexistent left bundle branch block or from infarction of the Purkinje network in the left side of the septum. The latter alternative was favored because it corresponded better with the location of the infarct at autopsy. The absence of diagnostic changes in the RS-T segment and T wave may have been due to preservation of the subepicardial half of the anteroseptal wall. Pulmonary emphysema, associated with anthracosis, may have been a factor in the low voltage in the axillary and limb leads.

CASE 82.—A 78-year-old man was admitted in coma with hemiplegia due to cerebral hemorrhage. He was known to have had hypertension, but no further history was obtainable. He died on the sixth hospital day of the cerebrovascular accident.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the fifth hospital day, after the administration of 0.4 Gm. of digitalis, is reproduced in Fig. 10, *D*. On the basis of a QRS duration of 0.12 second, an initial upright deflection in Leads $V_5$, $V_6$, and $aV_L$, and notching or slurring of the R wave in these leads, a diagnosis of left bundle branch block was made. In Leads $V_1$ through $V_3$ there was a minute initial R wave followed by a deep, broad, slurred S wave typical of the findings obtained through precordial leads over the right ventricle in cases of left bundle branch block. From a quick perusal of Lead $V_4$, the QRS complex would appear to consist of a deep, slurred Q wave and a small late R wave, fairly typical of the findings produced in this lead by infarction of the anteroseptal aspect of the apex. This was the interpretation placed upon Lead $V_4$ in the ante-mortem study of the tracing; however, the QRS duration in Lead $V_4$, as measured from the beginning of the major downstroke to the end of the descending limb of the R, was only 0.08 second, as compared with 0.12 second in other leads. More careful scrutiny revealed a small, slurred initial R wave 0.04 second in duration, which preceded the major downstroke. Thus, Lead $V_4$ actually showed an RSR′ complex, transitional in type between the right ventricular pattern recorded in Lead $V_3$ and the left ventricular in Lead $V_5$. All cycles of Lead $aV_F$ showed a broad, slurred QS complex, which, in the ante-mortem interpretation, was taken as evidence of coexistent posterior infarction. In view of the fact that the potential variations of the posterobasal aspect of the left ventricle were transmitted to both upper extremities to cause a comparable broad, slurred R wave in both Leads $aV_R$ and $aV_L$, it was more plausible to assume that the right ventricle rested on the diaphragm and that the broad, slurred QS complex of Lead $aV_F$ was representative of the findings often obtained over the normal right ventricle in cases of left bundle branch block. The standard leads also showed left bundle branch block with a QS complex in Leads II and III, which, like that in Lead $aV_F$, had two possible explanations.

*Pathologic Findings.*—The heart weighed 580 grams and showed three separate healed infarcts, as outlined in Fig. 13. A transmural infarct of the basal half of the posterior aspect of the left ventricle had caused considerable thinning of the wall. A second infarct involved the left side of the septum and the subendocardial half of the anterior and lateral walls in the second and third segments and the entire septal and anterolateral walls in the apical segment. A third small subendocardial anterolateral infarct in the fourth and fifth segments may have represented an upward extension of the apical infarct. Microscopic sections of all three infarcts showed dense fibrosis with residual islands of intact muscle. Although autopsy revealed both the anterior and posterior infarcts predicted in the ante-mortem interpretation of the electrocardiogram, there is considerable doubt, from a restudy of the tracing, that either diagnosis was justified. An RSR'

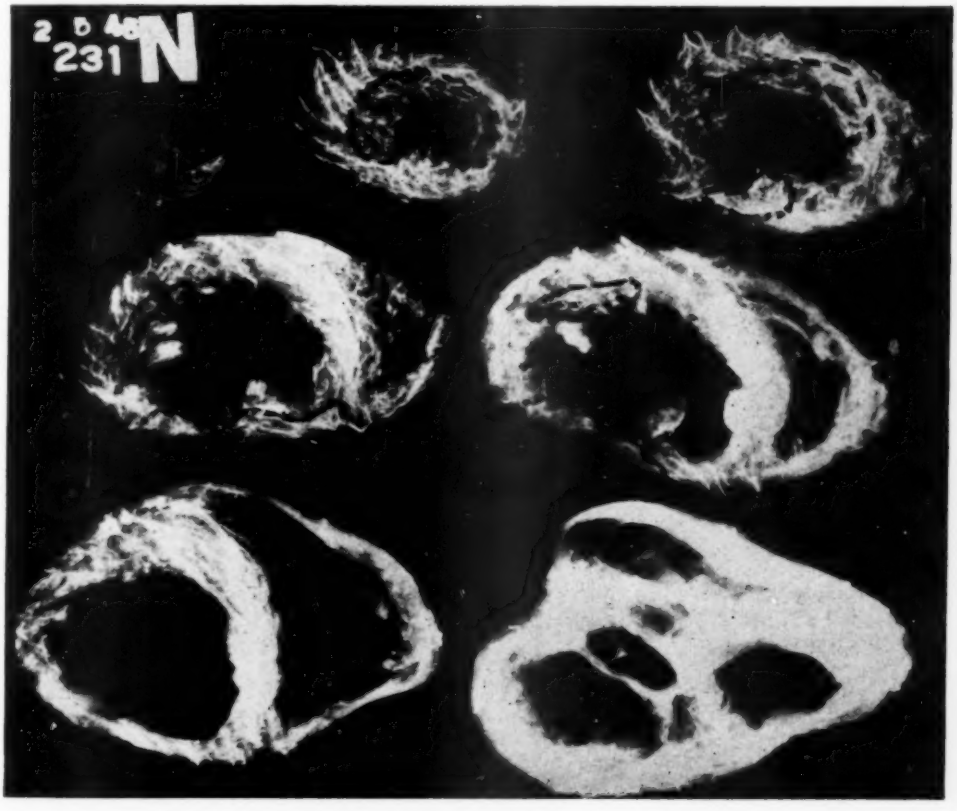


Fig. 13.—Roentgenogram of the injected heart in Case 82, showing position of old, healed anterolateral, septal, and posterior infarcts.

complex like that of Lead $V_4$ may occur at the transitional zone in left bundle branch block, uncomplicated by infarction, as will be emphasized in a subsequent communication. In the presence of left bundle branch block, it is difficult or impossible to make a diagnosis of old anterior infarction, since the potential of the left ventricular cavity is initially positive, thus causing a preliminary upright deflection in all semidirect leads over the left ventricle. The question remains as to whether the QS complex in Leads $aV_F$, III, and II was due to the posterobasal infarct found at autopsy or merely to the horizontal position of the heart with reference of the potential variations of the right ventricle to the left leg. In spite of the apparent correlation with the posterior infarct, it seems more likely that the QS complex was of right ventricular origin and that the

finding of the posterior infarct was merely fortuitous. Although the left side of the apical half of the septum was involved in the anterior infarct, the left bundle branch block was probably independent and due to an unrecognized lesion higher in the septum.

CASE 83.—A 56-year-old man was admitted to the hospital in a critical state with lobar pneumonia due to Friedländer's bacillus, complicated by fibrinous pericarditis. Past history was unobtainable. Death occurred from a pulmonary abscess twelve days after admission. No cardiac glycosides were given.

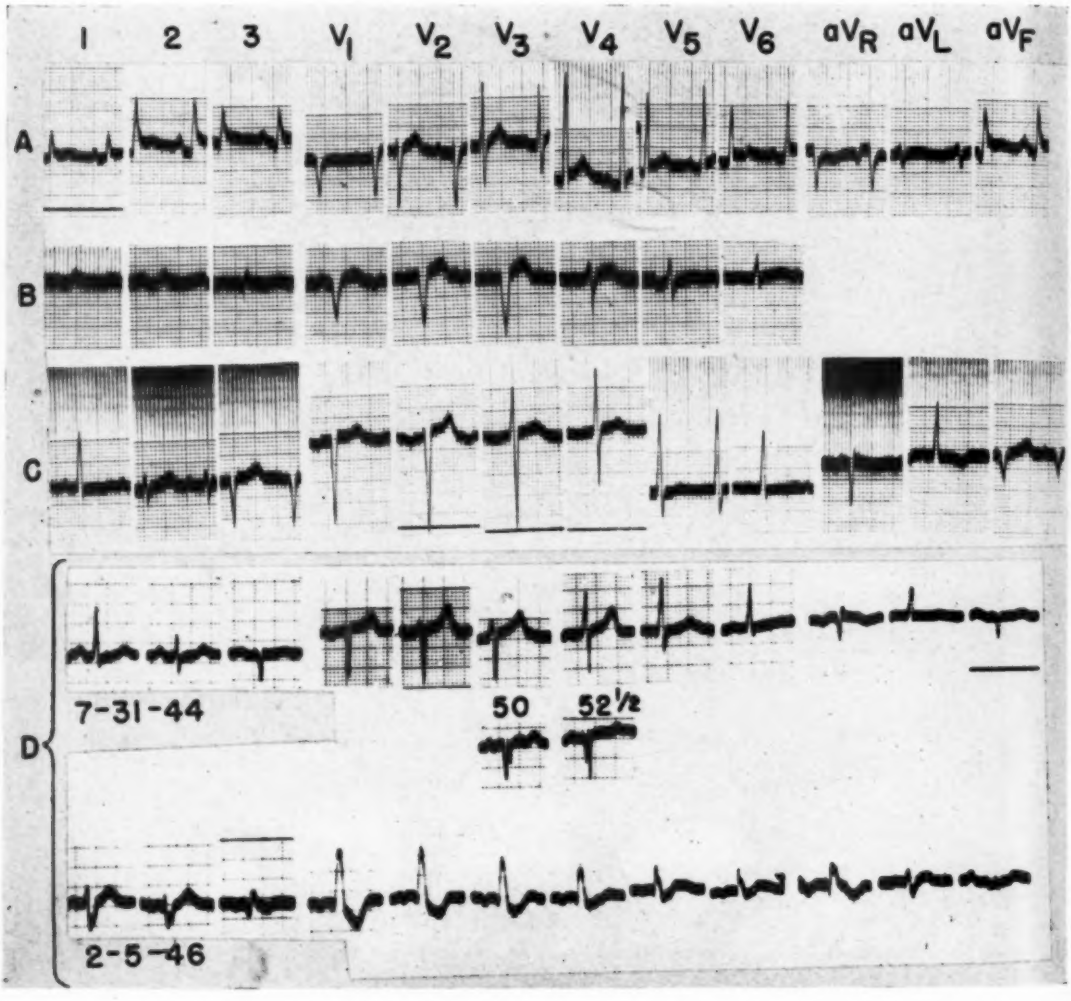


Fig. 14.—Healed primary septal infarction. *A*, Case 83; *B*, Case 84; *C*, Case 85; *D*. Case 86.

*Electrocardiographic Findings.*—Electrocardiograms obtained on the fifth and ninth hospital days were essentially the same, the former being reproduced in Fig. 14, *A*. The most striking finding was the elevation of the RS-T segment in Leads $V_4$ through $V_6$ and $aV_F$, the latter carrying over into Leads II and III. In view of the tall R wave without antecedent Q wave in Leads $V_4$ through $V_6$ and the upward concavity of the RS-T segments, the displacement in these leads was attributed to acute pericarditis. A Q wave was present in Lead $aV_F$, but was only 0.02 second in

duration and 15 per cent of the amplitude of the succeeding R wave. For this reason and because of the particularly characteristic contour of the RST-T complex in Lead $aV_F$, the findings in this lead were also attributed to pericarditis. Leads $V_{3R}$ and $V_1$ displayed a QS complex, which was notched near its onset, and Lead $V_2$, which also reflected the potential variations of the right ventricle and right side of the septum, exhibited a Q wave of 1.0 mm., an R wave of 1.0 to 3.0 mm., and an S wave of 8.0 to 13.0 millimeters. Although a smooth QS deflection may occur as a normal variant in these leads, a Q wave followed by a small R wave or R-wave equivalent (notch) and then by a deep S wave is abnormal and is representative of infarction of the septum. The septal infarct was considered healed because of the absence of T-wave abnormalities in Leads $V_{3R}$, $V_1$, and $V_2$. The standard leads were diagnostic of pericarditis, but revealed no evidence of septal infarction.

**Fig. 15.—Roentgenogram of the injected heart in Case 83, showing position of old, healed primary septal infarct.**

*Pathologic Findings.*—The heart weighed 526 grams and showed a universal acute fibrinous pericarditis and a 400 c.c. effusion. A well-vascularized, healed, patchy infarct was found in the apical half of the septum, extending for a short distance into the anteroseptal wall of the left ventricle, as shown in Fig. 15. The failure of the posterolateral portion of the left ventricle to inject was due to a technical error, since sections revealed no evidence of infarction in this region. It is noteworthy that the infarction was limited to the apical half of the septum, whereas the electrocardiographic signs were confined to Leads $V_{3R}$, $V_1$, and $V_2$. This discrepancy was attributable to the position of the transitional zone between Leads $V_2$ and $V_3$ and, hence, to the fact that Leads $V_{3R}$, $V_1$, and $V_2$ were the only leads reflecting the potential variations of the right ventricle and right side of the septum. The R wave or notch in these leads was presumably produced by activation of the outer wall of the right ventricle, and the antecedent Q wave could

be correlated with the septal infarction found at autopsy and was probably a manifestation of reversal in the direction of septal activation. The continuation of the septal infarct for a short distance into the subendocardial portion of the anterior wall of the left ventricle was not evident electrocardiographically. The slight extension into the posteroseptal wall was probably not a factor in the production of the normal Q wave recorded in Lead $aV_F$.

CASE 84.—A 54-year-old diabetic man noted his first cardiovascular symptoms three months before hospital admission, when he had an attack of prolonged constrictive retrosternal pain and dyspnea which required morphine. Since then he had several transient attacks, generally relieved by nitrites. He was admitted in left ventricular failure two hours after the onset of a more severe retrosternal pain, which had failed to respond to nitrites. Death occurred on the fifth hospital day.

*Electrocardiographic Findings.*—An electrocardiogram obtained seven hours before death and after the administration of 1.8 mg. of Cedilanid on the three preceding days is reproduced in Fig. 14, *B*. The QRS complexes in both the precordial and extremity leads showed no essential difference from those in three preceding tracings. Although a first glance raised the question of a conduction defect, the measurement of the QRS complex did not exceed 0.10 second and the slurring in the extremity leads was of the type customarily found in the presence of low voltage. The QR complex and inverted T wave of Lead $aV_F$ were strongly suggestive of posterior infarction, but because of a borderline ratio and low voltage, an unequivocal diagnosis was not justified. A slurred QS complex was found consistently in Leads $V_{2R}$, $V_1$, $V_2$, and $V_3$. An initial upright deflection was present constantly in Leads $V_4$ through $V_7$. The R wave was low in voltage in these leads, but increased progressively at the expense of the S wave as the electrode was moved from Position $V_4$ toward the left. The question arose as to whether the absence of the R wave in Leads $V_1$ through $V_3$ was due to infarction of the septum or whether it was a variant sometimes encountered in precordial leads over the right ventricle in cases of left ventricular hypertrophy. If a posterior infarct had been present, as suggested by the findings in Lead $aV_F$, an accentuation of the R wave would have been expected in precordial leads. Thus, an infarction of the septum, which obliterated the positive potentials ordinarily referred to the right side of the precordium during septal activation, seemed the more plausible explanation for the QS pattern in leads from the right side of the precordium. Since an initial R wave was present in Lead $V_4$ and all leads farther to the left, there was no electrocardiographic evidence of infarction of the anterolateral wall of the apex.

*Pathologic Findings.*—The heart weighed 310 grams and exhibited a large infarct which extended in patchy fashion through the entire length of the septum and continued backward into the subendocardial half of the posteroseptal wall in all segments and into the subendocardial half of the anteroseptal wall in the apical fourth of the left ventricle. Thus, the position of the infarct was like that in Case 75, shown in Fig. 7, with the following exceptions: the septal lesion was present in the apical segment and extended into the anteroseptal wall of this segment in the same fashion as in the second segment of Fig. 7 and also extended into the entire length of the posteroseptal wall in the same fashion as in the basal half of Fig. 7. The bulk of the infarct was judged to be of more than one month's duration, but patchy areas of recent reinfarction were discernible microscopically. Although the septal involvement in this case was more extensive than in some of the cases of right bundle branch block, the QRS interval was within normal limits. The absence of the initial R wave in Leads $V_{2R}$, $V_1$, $V_2$, and $V_3$ was probably a manifestation of the septal infarction, and the QR pattern in Lead $aV_F$ was apparently a result of the posterior infarct. The extension of the infarct into the anteroseptal aspect of the apex may have been a factor in the QS complex recorded in Lead $V_3$ and should have resulted in an abnormal Q wave in Lead $V_4$, as well. The absence of infarction of the lateral wall of the apex was in keeping with the initial R wave in Leads $V_5$ through $V_7$.

CASE 85.—A 79-year-old woman was admitted to the hospital in coma with right hemiplegia due to cerebral hemorrhage. She was known to have had hypertension, but no further past history was obtainable. Death occurred on the ninth hospital day from the cerebral vascular accident. No cardiac glycosides were given.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the second hospital day is reproduced in Fig. 14, *C*. The QRS interval was 0.08 second, the initial deflection was upright in all precordial leads, and the R wave showed the normal increase in amplitude and duration as the electrode was moved from Position $V_1$ to $V_6$. The inversion of the T wave in Lead $aV_L$, together with the flattening in Leads $V_5$ and $V_6$, raised the question of left ventricular hypertrophy, but an unequivocal diagnosis could not be made, since the time interval from the beginning to the peak of the R wave in these leads was within normal limits. All cycles of Lead $aV_F$ showed a QS complex with a slurred descending limb, requiring 0.04 second from onset to nadir. The question arose as to whether this QS complex was a manifestation of an old healed infarct of the posterior wall of the left ventricle or was due to transmission of the potential variations of the right ventricle to the left leg, as a result of horizontal position of the heart. Although a positive differentiation could not be made, the former alternative was favored in the ante-mortem interpretation of the tracing. Repetition of Lead $aV_F$ in different postures, as well as esophageal leads, would have been helpful in reaching a definite decision.

*Pathologic Findings.*—The heart weighed 390 grams and showed moderate concentric left ventricular hypertrophy. There was an old, completely healed, patchy infarct of the interventricular septum, almost identical in position, size, and shape to that in Case 83, Fig. 15. The relatively small initial R wave of Leads $V_1$ and $V_2$ may have been derived from islands of uninfarcted muscle in the septum or from the outer wall of the right ventricle. Although the infarct extended into the posterior aspect of the apical two segments in a manner almost identical with that of Fig. 15, it is doubtful that this limited area of involvement could have accounted for the QS complex of Lead $aV_F$. The other alternative of horizontal position with transmission of potential variations of the right side of the septum and right ventricle to the left leg seemed the more likely explanation for the QS complex recorded in Lead $aV_F$. In view of the slurring and prolongation of its descending limb, this QS complex was probably a manifestation of the septal infarct.

CASE 86.—A 74-year-old man with diabetes mellitus and hypertension was first admitted to the hospital on July 26, 1944, in congestive failure. During the remaining twenty months of his life, he was troubled with exertional dyspnea and recurrent cardiac failure, for which he had been hospitalized elsewhere. No definite history of angina pectoris or myocardial infarction was elicited. He was readmitted in cardiac decompensation in April, 1946, and had an uneventful course until the ninth hospital day, when he suddenly died.

*Electrocardiographic Findings.*—Electrocardiograms taken on July 29, 1944, before the administration of digitalis, and on Feb. 5, 1946, while the patient was on maintenance doses, are reproduced in Fig. 14, *D*. The tracings taken during the first admission showed a small, brief initial R wave and a prominent S wave in right ventricular Leads $V_1$ through $V_3$, and a minute Q wave, prominent R wave, and late intrinsicoid deflection (0.06 second after onset of the QRS complex) in left ventricular Leads $V_5$, $V_6$, and $aV_L$. These findings were attributed to left ventricular hypertrophy. Lead $aV_F$ exhibited a QS complex, strongly suggestive of posterior infarction, but not diagnostic because of its brief duration and low voltage. In standard Lead III there was a small, slurred initial R wave which was evidently derived from the initial negativity of the left arm. Thus, the standard leads showed no evidence of posterior infarction. For further evidence, esophageal leads were obtained. Judging from the contour of the P wave in Leads $E_{50}$, $E_{52}$, and $E_{55}$, the electrode was behind the ventricle and a short distance below the auriculoventricular groove. The W-shaped QRS complex registered in these leads was regarded as diagnostic of posterior infarction and thus confirmatory of the findings in Lead $aV_F$. From the contour of the T wave, the posterior infarct was considered to be old and healed. In the tracing of Feb. 5, 1946, there was a striking change in the first four precordial leads, characterized by the appearance of a tall R wave and late intrinsicoid deflection, together with RS-T depression and T-wave inversion, indicative of right bundle branch block. Because of the presence of a distinct Q wave in these leads, the right bundle branch block was attributed to infarction of the septum. The electrode at Positions $V_3$ and $V_4$ was believed to be over the right side of the heart, not only because of the similarity of the QRS pattern to that in Leads $V_1$ and $V_2$, but also because of the

inversion of the sinus P waves in all four leads. The diphasic P waves in Leads $V_5$ and $V_6$ and the shift in the slurring to the descending limb of the R wave suggested that these leads were at the transitional zone. Thus, the Q wave in all six precordial leads could have been a manifestation of an infarct limited to the septum. Lead $aV_L$ displayed an initial R wave, a broad, slurred S wave, and upright T wave, which is representative of the pattern registered in precordial leads over the left ventricle in cases of right bundle branch block. The initial downward deflection in Leads $aV_F$, II, and III was considered a remnant of the old posterior infarct. Thus, the old posterior infarct was recognizable in Lead $aV_F$ and a subsequent infarct of the septum in precordial leads. The changes in the RS-T segments and T waves were attributed to superimposed digitalis effect. In a final tracing, taken one week before death, the QRS pattern in leads from the right side of the precordium showed no essential change, but the transitional zone had shifted sufficiently to the right so that Leads $V_5$ and $V_6$ exhibited an initial R wave, a slightly delayed intrinsicoid deflection, and a subsequent broad, slurred S wave, typical of the findings in left ventricular leads in left ventricular hypertrophy, complicated by right bundle branch block.

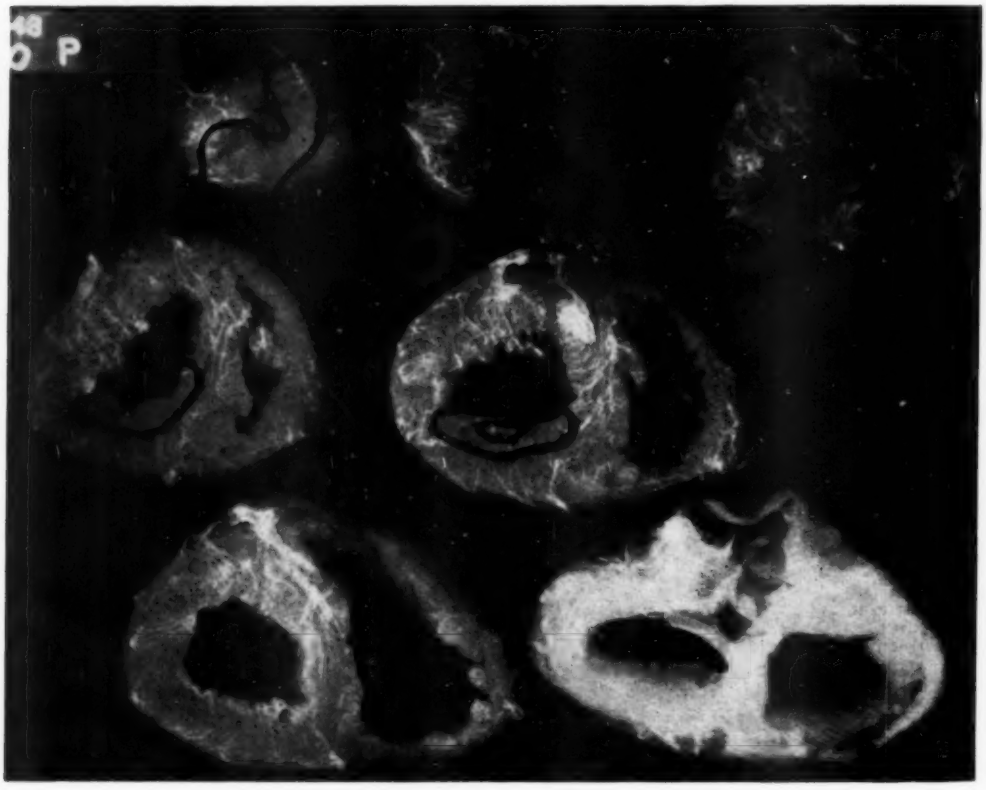


Fig. 16.—Roentgenogram of the injected heart in Case 86.

*Pathologic Findings.*—The heart weighed 753 grams and exhibited an old healed infarct, which was confined to the subendocardial half of the posterior wall in the fourth and fifth segments and extended from the posterior wall through the interventricular septum into the subendocardial portion of the anteroseptal region in the apical three segments, as outlined in Fig. 16. The infarct was well fibrosed throughout and appeared confluent from the posterior wall into the septum. Despite the lack of pathologic demarcation, it is probable, from the serial electrocardiograms, that the posterior portion was present in July, 1944, and accounted for the changes in Lead $aV_F$ and

the esophageal leads, and that the septal portion developed some time during the next one and one-half years and produced right bundle branch block. The distribution of the septal infarct at autopsy was in keeping with the interpretation of the tracing of Feb. 5, 1946.

## COMMENT

*Classification of Pathologic Findings Referable to Septal Infarction.*—The material to be summarized comprises eighty-nine cases in which infarction was demonstrated at autopsy in one-third or more of the interventricular septum. The series was classifiable pathologically into three main groups: Group A, primary septal infarction, six cases; Group B, septal involvement associated with extensive anterior or anteroposterior infarction, fifty-nine cases; Group C, septal continuation of posterior infarction, twenty-four cases.

In Group A, the lesion classed as a primary septal infarction was distributed in patchy fashion through the entire septum in one patient (Case 84), through the basal four-fifths in one patient (Case 75), and was limited to the apical half in three patients (Cases 83, 85, and 86), and to the middle half in one patient (Case 76). It continued subendocardially for a very short distance into the anteroseptal and posteroseptal walls in all patients and was confluent with an independent posterior infarct of different age in two patients (Cases 75 and 86). Electrocardiographic studies were made during the acute stage of the septal lesion in two patients (Cases 75 and 76) and only after healing in the other four patients.

The major portion of the lesion in the fifty-nine cases of Group B was located in the free anterior and anterolateral walls of the left ventricle, but the infarct continued into the apical one-third or more of the septum, often reaching the free posterior wall. The series was divisible into three subgroups, in accordance with the extent of the septal portion of the lesion: (1) Infarction confined to the apical third. This distribution was found in six patients (Cases 22, 42, 43, 64, 67, and 96). The lesion was further limited to the left side of the septum in five of the foregoing patients, but was transseptal in one (Case 22). The infarct was recent in Case 22 and healed in the remainder. (2) Infarction occupying the apical one-half to two-thirds of the septum. This distribution was found in thirty-one patients (Cases 29 through 33, 37, 41, 46, 47, 48, 50 through 58, 61, 62, 63, 65, 66, 69, 73, 77, 79, 81, 82, and 91). The lesion was confined to the left side of the septum in twelve of the foregoing patients and to the anterior half in three. In the other sixteen patients, the lesion in the apical third or more of the septum extended from one endocardial surface to the other and from the anterior to the posterior terminus, but near its upper boundary the infarct usually tapered off to occupy the left side of the anterior portion of the septum. The infarct within these boundaries was not necessarily complete and often was patchy in distribution. Electrocardiographic studies were made during the acute stage in seventeen patients and after healing in the other fourteen. (3) Infarction involving more than the apical two-thirds of the septum. This distribution was found in twenty-two patients (Cases 23 through 27, 34, 35, 36, 38, 39, 40, 49, 59, 70, 71, 72, 74, 78, 80, 151, 152, and 153). The infarct was confined to the left side of the septum in four of the

foregoing patients and to the anterior half in two. In the remainder, the lesion was transseptal in the apical half or more, but tended to narrow to the left side of the anterior portion in the basal one-half to one-third of the septum. The infarct was recent in eighteen patients and healed in four.

The infarct in the twenty-four cases of Group C involved the posterior wall of the left ventricle primarily and continued into the posterior portion of the septum. The cases were classifiable into three subgroups, according to the location and extent of the septal lesion: (1) Infarction of the apical one-third to two-thirds of the septum. This distribution was present in six patients (Cases 99 through 102, 111, and 114). The lesion represented an extension of a posteroapical infarct and was confined to the posterior one-third to one-half of the septum in four patients and to the left side in two. (2) Infarction of the basal one-third to two-thirds of the septum. This distribution was present in twelve patients (Cases 87, 89, 90, 92, 103, 108, 121, 125, 126, 127, 128, and 136). The lesion was confined to the posterior one-third to one-half of the septum in all patients and to the left side, as well, in seven. (3) Infarction extending the entire length of the septum. This distribution was present in six patients (Cases 60, 88, 95, 104, 110, and 124). The lesion was limited to the posterior one-third to one-half of the septum in all patients and to the left side in three.

*Classification of Electrocardiographic Findings Associated With Septal Infarction and Correlation With Pathologic Findings.*—The electrocardiographic patterns encountered in the series of eighty-nine cases were classifiable into one or more of the following categories: (1) auriculoventricular block; (2) right ventricular conduction defects; (3) left ventricular conduction defects; (4) Q waves and/or RS-T segment displacement in right ventricular leads directly referable to, or at least suggestive of, septal infarction; (5) absence of direct evidence of a septal lesion.

The QRS interval was 0.12 second or more in the thirty cases classified primarily into combined Classifications 2 and 3, whereas the measurement was less than 0.12 second in the remaining fifty-nine cases falling into combined Classifications 4, 5, and 6. The expected trend toward larger septal infarcts in cases with prolonged QRS interval than in cases with normal QRS interval was not borne out at autopsy. The lack of significant difference in the size of the septal infarcts in the two groups may have been due to the fact that the prolongation of the QRS complex in the majority of the thirty cases was believed to have been independent of the septal infarct. Further consideration of electrocardiographic-pathologic correlations will be deferred to the discussion of each individual group.

1. *Auriculoventricular Block*: Complete A-V block was found in four patients (Cases 25, 88, 96, and 104). It was associated with auricular tachycardia in Cases 96 and 25 and was undoubtedly independent of the infarct confined to the apical one-third of the septum in the former and may have been unrelated to the massive septal extension of an anterior infarct in the latter. Complete A-V block was associated with a sinus tachycardia, averaging 140 beats per minute, in Case 88 and with auricular fibrillation in Case 104, but was

believed referable to an extension of a large recent posterior infarct into the base of the septum in both cases. A transient A-V nodal tachycardia with a 2:1 ratio and a terminal auricular flutter with similar ratio were found in Case 87, but sinus rhythm with a normal P-R interval was also observed in this case, despite the fact that the posterior half of the base of the septum exhibited transmural infarction, complicated by a 3.0 cm. perforation. Twelve other cases were observed with sinus rhythm during life and infarction of the posterobasal portion of the interventricular septum at autopsy and it is noteworthy that the P-R interval was 0.20 second or less in each case.

2. *Right Ventricular Conduction Defects*: Defects of this type were found in a total of fourteen patients, including three with primary septal infarction (Cases 75, 76, and 86), nine with primary anterior infarction (Cases 54, 69 through 74, 78, and 153), and two with primary posterior infarction (Cases 87 and 110). The conduction defect was established in all cases by the demonstration of a QRS interval of 0.12 second or longer in complexes derived from impulses of supraventricular origin and was localized to the right ventricle by the presence of a prominent late R wave in leads over the right side of the heart, together with an abnormally delayed intrinsicoid deflection, commencing 0.08 second or more after the onset of the QRS complex.

The QRS-T pattern in the precordial leads of one patient (Case 110) was similar to that of uncomplicated right bundle branch block, and the conduction defect in this case was probably independent of the patchy infarct of the left side of the posterior third of the septum found at autopsy. One other patient (Case 153) displayed a transient right bundle branch block manifested by an exceptionally tall initial R wave and a markedly depressed RS-T junction in Leads $V_1$ and $V_2$ and by a small Q wave and a tall late R wave in right ventricular Lead $V_3$. The findings in the first two precordial leads were more in keeping with the transient right bundle branch block which sometimes accompanies acute left ventricular failure, but the findings in Lead $V_3$ were strongly suggestive of the acute septal infarction found at autopsy.

Following the established custom, the term "right bundle branch block" was used to characterize the conduction defect in the individual reports of the other twelve cases. In the strict sense, this terminology was incorrect since (1) the QRS-T abnormalities were directly referable to a septal lesion, but differed significantly from the pattern in uncomplicated right bundle branch block; (2) the infarction in some of the cases involved the apical portion of the septum and spared the anatomical site of the right bundle branch.

The QRS-T pattern in right ventricular leads of these twelve cases exhibited distinctive features which differed from the pattern of uncomplicated right bundle branch block in one or both of the following respects: (a) the direction of the initial phase of the QRS, (b) the position of the RS-T junction. The initial upstroke characteristically recorded in right ventricular leads in uncomplicated right bundle branch block represents positive potentials derived from septal activation and transmitted to the right ventricular cavity and right precordium. The replacement of this initial R wave by an abnormal Q wave occurs as a manifestation of the conduction defect associated with sep-

tal infarction when negative potentials transmitted from the left ventricular cavity through the infarcted septum to the right precordium exceed positive potentials coming from activation of intact remnants of the septum. A distinct Q wave, a late R wave, and an abnormally delayed intrinsicoid deflection were demonstrated in right ventricular leads of ten patients (Cases 69, 70, 72, through 76, 78, 86, and 87) and were considered diagnostic of septal infarction in all cases, with the possible exception of Case 87. The right ventricular conduction defect developed terminally in this patient in association with auricular flutter and a ventricular rate of 176. The possibility of obliteration of the customary initial R wave from Lead $V_1$ by the flutter wave was deemed unlikely, but could not be excluded positively. A minute initial R wave was present in right ventricular Leads $V_1$ through $V_3$ in Cases 54 and 71, but the conduction defect was ascribed to acute septal infarction because of the presence of classical upward displacement of the RS-T segment. Whereas uncomplicated right bundle branch block usually causes depression of the RS-T junction in leads from the right precordium, the right ventricular conduction defect associated with acute septal infarction was manifested by an elevated or at least an isoelectric RS-T junction in these leads in eleven of the cases.

The septal portion of the infarct at autopsy was limited to the apical half of the septum in two patients (Cases 73 and 86), to the middle half in one (Case 76), to the apical two-thirds in two patients (Cases 54 and 69), and thus failed to reach the anatomic site of the right branch of the bundle of His. The position of the lesion in these five cases suggested that the late arrival of the impulse at the epicardial surface of the free wall of the right ventricle was due to interruption of conduction through the Purkinje network beneath the endocardium of the right side of the septum rather than through the right branch of the bundle of His. If this premise be correct, the conduction defect in these cases was not a right bundle branch block in the strict sense of the term. On the other hand, the septal portion of the infarct in Case 87 was confined to the posterior half of the basal part of the septum. If this lesion was responsible for the terminally developing delay in arrival of the impulse at the epicardial surface of the right ventricle, its anatomic position suggested that it acted by interruption of conduction through the right bundle branch. The infarct in the other six cases involved more than the apical two-thirds of the septum and may have caused delay in the arrival of the impulse at the epicardial surface of the right ventricle, either by involvement of the right bundle branch or by destruction of the Purkinje network beneath the endocardium of the right side of the septum. Since the abnormal Q wave, the tall R wave, and the late intrinsicoid deflection due to septal infarction that has involved the right branch of the His bundle constitute a pattern which is indistinguishable from that due to infarction that has spared this portion of the septum, we shall continue to employ the customary term, right bundle branch block due to septal infarction, to designate this pattern.

The small but definite initial R wave in Leads $V_1$ through $V_3$ in Case 54 and the probable small initial R wave in the same leads in Case 71 require further discussion. Autopsy disclosed a recent transmural infarct, involving the

apical half of the anterior wall and septum and the apical one-third of the lateral and posterior walls in the former case, and a recent transmural infarct in the latter case, which was similar in distribution, but approximately one and one-half times as large. The right bundle branch block and RS-T segment displacement in Leads $V_1$ through $V_3$ were attributable to the septal infarct and the atypical initial R wave could be explained when consideration was given to the factors governing the direction of the first phase of the QRS complex under these circumstances. Whether or not a Q or R wave is recorded depends upon (1) the relative size of the preserved and infarcted portions of the septum, and (2) the magnitude of the opposing negative potentials developing in the left ventricular cavity during activation of residual living septal muscle. The initial negativity of the left ventricular cavity is normally due to the early arrival of the impulse and early onset of activation of the left side of the septum and anteroseptal wall of the left ventricle. When a portion of the septum is infarcted, these initial negative potentials are transmitted through the infarct to the right ventricular cavity to oppose the positive potentials simultaneously developing therein as a result of activation of preserved remnants of the septum. Infarction of most of the anterior wall and septum in both cases probably postponed the development of significant negativity in the left ventricular cavity for a brief interval, during which weak positive potentials referred to the right ventricular cavity from activation of the intact posterobasal portion of the septum were recorded as a small R wave. This was replaced by a deep downstroke as soon as the impulse reached and began to activate the uninfarcted basal portions of the posterior and lateral walls of the left ventricle.

After the establishment of the diagnosis of right bundle branch block due to septal infarction, further study of the electrocardiogram is indicated for evidence of extension of the lesion into the free anterior and posterior walls of the left ventricle. The recognition of associated infarction of the anterior wall depends upon identification of the transitional zone and examination of thoracic leads farther to the left. The detection of extension into the posterior wall is even more difficult, depending upon the interpretation of Lead $aV_F$ in the light of the findings in the precordial leads.

The decision as to the presence or absence of associated infarction of the anterior wall of the left ventricle is not difficult when the transitional zone is situated somewhere between precordial Positions 1 and 4, since the customary precordial leads then afford adequate exploration of the anterolateral wall of the left ventricle. This is illustrated by an analysis of the findings in Cases 76 and 75, in contrast to those in Cases 69 and 74. The transitional zone in Case 76 was located at precordial Position 2 because of the registration of a small quadriphasic QRS in Lead $V_2$. Leads $V_3$ through $V_6$ reflected the potential variations of the left ventricle and displayed a small initial R wave and a broad S wave typical of the findings over the normal left ventricle in right bundle branch block, from which it was concluded that the septal infarct did not extend significantly into the anterior wall of the left ventricle. The transitional zone in Case 75 was broader, covering both the $V_2$ and $V_3$ positions, as evidenced by a QRS-T pattern in Leads $V_2$ and $V_3$, which was intermediate between that in

right ventricular Lead $V_1$ and left ventricular Leads $V_4$ through $V_6$. The absence of Q waves from the last three precordial leads indicated that the septal infarct in Case 75 did not extend significantly into the anterior wall of the left ventricle. These conclusions were confirmed at autopsy in both cases. The QRS-T pattern in Lead $V_1$ in Cases 74 and 69 (tracing of December 1) was closely comparable with that in Lead $V_1$ in Cases 76 and 75, and the transitional zones were located at Position $V_2$, as evidenced by a less delayed intrinsicoid deflection and a succeeding S wave in Lead $V_2$. The abnormal Q waves and elevation of the RS-T segment in left ventricular Leads $V_4$ and $V_5$ in Cases 74 and 69 contrasted sharply with the findings in corresponding leads in the two previous cases and indicated that the septal infarct continued into the anterior and anterolateral walls of the left ventricle. This conclusion was confirmed at necropsy in both cases.

The transitional zone usually is located well to the right of the midclavicular line in uncomplicated right bundle branch block, but is not infrequently displaced to the left of this position in right bundle branch block due to septal infarction. Diagnostic difficulties arise under these circumstances, due to the fact that Leads $V_3$, $V_4$, and perhaps even $V_5$ reflect principally the potential variations of the right side of the septum and right ventricle rather than the left side of the septum and left ventricle. The abnormal Q wave, late R wave, and delayed intrinsiocoid deflection in Leads $V_3$ through $V_5$ of Case 86 was not due to infarction of the anterior wall of the left ventricle, but rather to septal infarction with right bundle branch block and displacement of the transitional zone to the left, as shown by the similarity in shape of the QRS complex and time of onset of intrinsicoid deflection to that in Lead $V_1$ and also supported by the finding of inverted sinus P waves in Leads $V_1$ through $V_4$, indicating proximity of the electrode to the right atrium. The absence of significant extension into the anterolateral wall of the left ventricle of this patient was suggested by the normal initial R wave in left ventricular Leads $V_6$ and $aV_L$. This was confirmed at necropsy.

Displacement of the transitional zone into the axilla may conceal signs of infarction of the free anterior wall of the left ventricle. For example, the abnormal Q wave and tall late R wave in the first five precordial leads in Case 72 were chiefly representative of the potential variations of the epicardial surface of the right ventricle, as shown by the synchronism of the intrinsicoid deflections. Since Lead $V_6$ revealed a small quadriphrasic QRS complex typical of the transitional zone and Lead $aV_L$ revealed a QR pattern of right ventricular origin, resembling that in Lead $V_2$, the customary precordial leads did not provide adequate exploration of the anterolateral wall of the left ventricle and additional leads would have been required to make the diagnosis of the associated infarction of the anterolateral wall of the left ventricle found at autopsy. The QR complex in Leads $V_4$ and $V_5$ in Case 73 differed in contour from that in Leads $V_1$ through $V_3$, but the simultaneous onset of the intrinsicoid deflection in these five leads indicated that the findings in Leads $V_4$ and $V_5$ were referable to infarction of the septum rather than the anterior wall of the left ventricle. Because of the frequency of leftward displacement of the transitional zone in

association with right bundle branch block due to septal infarction, additional leads, particularly $V_7$ and $V_8$, should be obtained.

Errors in the interpretation of the findings in Leads $aV_L$ and $aV_F$ are especially prone to occur in cases of right bundle branch block due to septal infarction, unless due cognizance is taken of cardiac position. Septal infarction may be manifested by an abnormal Q wave and a late R wave in Lead $aV_L$ when the heart is in the vertical position, due to predominant transmission of the potential variations of the right side of the septum and epicardial surface of the right ventricle to the left arm. Thus, the initial Q wave and late R wave in Lead $aV_L$ in Case 72 were referable to septal rather than lateral infarction, as shown by the correspondence in the contour of the QRS complex and time of onset of the intrinsicoid deflection with that in right ventricular Lead $V_2$. Vertical position was confirmed in this case by the registration of a relatively narrow R wave and broad S wave in Lead $aV_F$, typical of the findings obtained over the left ventricle in the presence of right bundle branch block. Septal infarction may be manifested by a small notched or W-shaped QS complex in Lead $aV_L$ when the heart is in semivertical position, due to predominant transmission of the potential variations of the transitional zone at the junction of septum and anterior wall to the left arm. This interpretation of the notched QS complex recorded in Lead $aV_L$ of Case 75 was borne out by autopsy, which revealed infarction of the septum, but not of the lateral wall of the left ventricle.

Septal infarction may be manifested by an abnormal Q wave and a late R wave in Lead $aV_F$, when the heart is in a horizontal position, due to predominant transmission of the potential variations of the right side of the septum and epicardial surface of the right ventricle to the left leg. Thus, the abnormal QR pattern in Lead $aV_F$ (and also in Leads II and III) of Case 74 was referable to septal rather than posterior infarction, as shown by the correspondence in contour of the QRS complex and time of onset of the intrinsicoid deflection with that in right ventricular Lead $V_1$. Horizontal cardiac position was verified in this case by the registration of a relatively narrow R wave and a broad S wave in Lead $aV_L$, typical of the findings obtained over the left ventricle in the presence of right bundle branch block. On the other hand, a diagnosis of septal infarction, extending into the posterior wall of the left ventricle, could be made in Case 69 from the registration of an abnormal QR pattern in Leads $aV_F$, III, and II, which differed significantly from the abnormal QR pattern of septal origin in Lead $V_1$, both as to duration of the Q wave and time of onset of the intrinsicoid deflection. Signs of the posterior extension were detectable in Case 69, because of an intermediate cardiac position favorable to the transmission of the potential variations of the posterior wall of the left ventricle to the left leg.

The standard leads showed classical signs of right bundle branch block in ten cases, atypical signs in keeping with this diagnosis in two cases, and evidence pointing toward left bundle branch block in two cases. It is noteworthy that the findings in the standard leads were not sufficiently distinctive in any case to permit a definite diagnosis of septal infarction as the cause of the conduction defect.

3. *Left Ventricular Conduction Defects*: These defects were established from the following findings: QRS interval of 0.12 second or longer in complexes derived from impulses of supraventricular origin; prominent late R wave and abnormally delayed intrinsicoid deflection in leads from the left axilla, which reflected the potential variations of the epicardial surface of the left ventricle. The sixteen patients whose electrocardiograms conformed with the foregoing criteria were classifiable into two groups, in accordance with the direction of the first phase of the QRS complex in precordial leads over the left ventricle: (a) those in whom an initial R wave was present in all precordial leads over the left ventricle, six patients (Cases 77, 82, 99, 114, 125, and 136); (b) those in whom a Q wave was present in one or more precoridal leads over the left ventricle, ten patients (Cases 43, 46, 50, 57, 59, 78, 79, 80, 95, and 96).

(a) *Pattern characterized by a QRS interval of 0.12 second or longer, and an initial R wave and a late intrinsicoid deflection in precordial leads over the left ventricle* are usually due to activation of the septum and left ventricle by impulses starting from the Purkinje network beneath the endocardium of the right side of the septum and progressing from right to left. This mode of activation causes (1) early positivity of the left ventricular cavity and thus an initial upstroke in precordial leads over the left ventricle; (2) late arrival of the impulse at the epicardial surface of the entire left ventricle, especially in its lateral and posterior aspects, with consequent prolongation of the ascending limb of the R wave and delay in the onset of the intrinsicoid deflection in left axillary leads.

From a study of the electrocardiographic and pathologic findings in Cases 77 and 125, it was concluded that the prolongation of the QRS complex in these cases was probably not due to the foregoing mechanism. The tracings were obtained four and twenty-three hours, respectively, after the onset of the pain and were followed shortly by death, with demonstration of an infarct of less than twenty-four hours' duration in the septum and lateral wall of the left ventricle. Although an initial upstroke was found in Leads $V_4$ through $V_6$, a distinct Q wave was recorded in left ventricular Lead $aV_L$ of both patients, indicating that the left ventricular cavity was initially negative and that the vector associated with septal activation pointed toward the right rather than than the left. Furthermore, the prolongation of the monophasic upright QRS complex recorded in Leads $V_4$ through $V_6$ of both patients appeared to be due more to spreading of the descending limb than to delay in the attainment of the peak of the R wave. These findings indicated that the lengthened QRS interval was due to the lateral, rather than the septal, portion of the lesion and were in keeping with an early infarct which had retarded, but not obliterated, the response to the activating impulse.

In the other four cases, the initial phase of the QRS complex was upright, not only in precordial leads over the left ventricle, but also in Lead $aV_L$, and the pattern conformed with that customarily attributed to left bundle branch block. Since the septal portion of the infarct was limited to the apical one-third in Cases 99 and 114 and to the apical one-half in Case 82, the conduction defect was probably due to a separate lesion in the left branch of the bundle of

His. An alternative explanation for the electrocardiographic findings in Case 81 was suggested by the pathologic demonstration of an acute infarct limited to the left side of the apical two-thirds of the septum. An infarct in this position may have interfered with spread of the impulse through the left Purkinje plexus into the septum and thus indirectly favored activation of the septum by impulses distributed through the right Purkinje plexus. This would have reversed the vector associated with septal activation, causing early positivity of the left ventricular cavity and thus an initial upstroke in leads over the left ventricle. A comparable reversal in direction of activation of septal remnants seemed the best explanation for the initial R wave recorded in all leads over an extensive transmural anterolateral infarction in Case 34, despite a QRS interval of only 0.10 second.

(b) *Patterns characterized by a QRS interval of 0.12 second or longer and an initial Q wave and late intrinsicoid deflection in precordial leads over the left ventricle* may be produced by (1) a conduction defect in the free wall of the left ventricle, resulting from dense infarction of the subendocardial portion and patchy infarction of the mid-zone and subepicardial layer; (2) left bundle branch block associated with a large septal infarct and accompanied by infarction of at least the deeper portion of the free wall of the left ventricle. Consideration will be given to the probable mechanism of production of the electrocardiographic findings in both types of conduction defect, prior to an analysis of the findings in the ten patients exhibiting these patterns, along with pathologic evidence of infarction of the septum and free wall of the left ventricle.

Abnormal QR complexes, delayed onset of the intrinsicoid deflection, and prolongation of the QRS interval were found in Cases 21, 45, 141, 154, and 155 as a manifestation of infarction involving the free wall of the left ventricle, but not the septum, and could be correlated with a lesion that was dense in the subendocardial layer and patchy in the more superficial portion of the myocardium. The downward component of the abnormal QR complex characteristic of infarction, distributed in the foregoing manner, represents negative cavity potentials transmitted to the overlying precordium while the impulse is making its way through the unresponsive subendocardial layer, whereas the succeeding upward component represents positive potentials referred to the surface after the impulse reaches and begins to activate living muscle in the mid-zone or subepicardial layer. Slurring or notching of the ascending limb of the R wave and prolongation of time interval from its onset to peak are prone to occur when the living muscle in the mid-zone or subepicardial layer is split up into islands by patches of dead muscle or fibrous tissue. The registration of a Q wave while the impulse is held up in the densely infarcted subendocardial muscle and a prolonged R wave during its retarded passage through patches of living muscle in the more superficial layers accounts for the lengthening in the interval preceding the intrinsicoid deflection and is an important factor in the prolongation of the QRS complex.

When left bundle branch block is accompanied by infarction of a portion of the septum, the left ventricular cavity receives positive potentials produced by activation of the intact remnants of septum and, at the same time, negative

potentials produced by activation of the right ventricle and transmitted to the right ventricular cavity and through the infarcted portion of the septum. The resultant initial potential of the left ventricular cavity depends first, upon the relative size of the infarcted and intact portions of the septum, and second, upon the magnitude of the negative potentials available for transmission through the septal infarct. Since the negative potentials referred to the right ventricular cavity during activation of its thin outer wall are much less than those referred to the left ventricular cavity during activation of its thick outer wall, one would surmise that a much greater septal destruction would be necessary for preponderant initial negativity of the left ventricular cavity in the presence of left bundle branch block than for preponderant initial negativity of the right ventricular cavity in the presence of right bundle branch block. Complicating right ventricular hypertrophy should accentuate the negative potentials transmitted through the infarcted septum in the presence of left bundle branch block and thus should favor the registration of Q waves in left ventricular leads. Furthermore, the recording of Q waves under these circumstances not only requires septal infarction of sufficient size to lead to initial negativity of the left ventricular cavity, but also infarction of at least the deeper portion of the myocardium beneath the exploring electrode.

In ten patients with a QRS interval of at least 0.12 second, an abnormal Q wave, and a late intrinsicoid deflection in left ventricular leads, infarction of both the septum and free wall of the left ventricle was demonstrated at autopsy and the question arose as to the site of the conduction defect.

Left bundle branch block was suggested by the findings in the standard limb leads in Case 78, but could be excluded indirectly by the demonstration of definite signs of right bundle branch block in the precordial leads, together with a normal P-R interval. If left bundle branch block also had been present, A-V block should have resulted. A small Q wave and a broad R wave were recorded in Lead $aV_L$, but only the upright phase carried over into Lead I, creating the false impression of left bundle branch block. The QR pattern in Leads $V_5$, $V_6$, and $aV_L$ of this patient was not a manifestation of right bundle branch block, because of differences in contour and time of onset of intrinsicoid deflection from that in right ventricular Leads $V_1$ and $V_2$, and thus, by exclusion, was ascribed to a conduction defect in the free wall of the left ventricle. The distribution of the lesion in the anterolateral aspect of the left ventricle confirmed these conclusions.

Left bundle branch block was considered very unlikely in Cases 43, 57, 59, 79, 95, and 96 because of the registration of distinct Q waves in left ventricular leads (indicating early negativity of the left ventricular cavity), together with a small initial R wave and a prominent S wave in Lead $aV_R$ (pointing to early positivity of the right ventricular cavity). However, left bundle branch block could not be excluded positively by these findings, since the initial R wave in Lead $aV_R$ might have been transmitted from the epicardial surface of the right ventricle, rather than from the cavity. The potential variations of the posterobasal portion of the left ventricle were referred to the right arm in Cases 46, 50, and 80, but the registration of normal initial R waves in leads from the

right precordium in the two former cases was somewhat against initial negativity of the right ventricular cavity secondary to left bundle branch block.

The septal infarct was excluded as a cause of the electrocardiographic findings in Cases 43 and 96, by reason of its limitation to the left side of the apical one-third of the septum. Localization of the conduction defect in the free wall of the left ventricle of these cases was supported by the close correspondence between the abnormal QR patterns and the distribution of the lesion in the underlying myocardium. It is noteworthy that a QRS interval of 0.16 second in Case 96 was apparently referable to a conduction defect in the free wall of the left ventricle.

The infarcts in Cases 46, 57, 79, and 95 involved approximately one-half of the septum and were thus comparable to the smallest infarcts in this series that had produced right bundle branch block. For reasons already given a larger septal infarct would probably be needed for initial negativity of the left ventricular cavity in the presence of left bundle branch block than for initial negativity of the right ventricular cavity in the presence of right bundle branch block. Since half of the septum was spared in each of these four cases, initial R, instead of Q, waves would have been expected in left ventricular leads if left bundle branch block had been present. Because of the aforementioned evidence against left bundle branch block together with the close correspondence between the QR patterns and the distribution of the lesion in the free wall of the left ventricle, it was concluded that the conduction defect in these cases was in the free wall. However, it must be admitted that a conduction defect in the septum could not be excluded positively.

The lesion in Cases 50, 59, and 80 involved two-thirds or more of the septum and thus was considered large enough to have accounted for initial negativity of the left ventricular cavity, if left bundle branch block had been present. The apparent initial positivity of the right ventricular cavity in the two latter cases was against the presence of left bundle branch block, but the initial negativity in Case 50 was compatible. However, if the extensive septal destruction in these patients had been complicated by left bundle branch block, a longer QRS interval would have been anticipated than the measurement of 0.12 second in Cases 50 and 80 and 0.13 second in Case 59. Since the pattern in leads facing the epicardial surface of the left ventricle of all three patients corresponded satisfactorily with the distribution of the lesion in the underlying myocardium, a conduction defect in the free wall was favored.

4. *Q Waves and/or Displacement of the RS-T Segment in Leads From the Right Precordium, in the Absence of Bundle Branch Block*: Activation of the septum and activation of the anterior wall of the right ventricle are jointly responsible for the initial R wave normally found in leads taken with the exploring electrode applied to the precordium over the right ventricle or atrium and repolarization of these structures presumably has the predominant effect upon the RS-T segment and T waves in the same leads. When the heart is in horizontal position, Lead $aV_R$ reflects chiefly the potential variations of the right side of the septum and posteroinferior wall of the right ventricle and is thus comparable to leads from the right precordium. Infarction of the septum,

in the absence of bundle branch block, may cause changes in the QRS and/or RS-T complex in right ventricular leads, which are classifiable into three main groups: (a) triphasic QRS complex, consisting of a small Q, small R, and deep S wave, with or without abnormal displacement of the RS-T segment; (b) monophasic QS deflection, with or without displacement of the RS-T segment; (c) normal RS complex with abnormal displacement of the RS-T segment.

(a) *Triphasic QRS complex in right ventricular Leads $V_1$ and/or $V_2$, characterized by a small Q, small R, and deep S wave in the absence of right bundle branch block** was encountered in one case of primary septal infarction (Case 83) and in three cases of septal extension of large anteroposterior infarction (Cases 50, 66, and 152). This pattern was well correlated with the pathologic demonstration of a healed infarct of the left side of the septum in Cases 66 and 152. The initial Q wave reflected early negativity of the right ventricular cavity, presumably due to activation of the preserved right half of the septum by impulses distributed through the right Purkinje system before impulses distributed through the corresponding network beneath the left ventricular endocardium could traverse the infarct and reach intact septal muscle. The succeeding R wave may have been due entirely to activation of the free wall of the right ventricle or partially to activation of septal remnants by impulses which finally arrived by way of the left-sided Purkinje system. The deep S wave represented negative potentials of the left ventricular cavity transmitted to the right precordium after depolarization of the septum and free wall of the right ventricle.

Right ventricular Lead $V_1$ in Case 50 displayed a 1.0 mm. Q wave, a 4.0 mm. R wave, and a slightly larger S wave. Autopsy disclosed a large, healed anterolateral infarct which involved the entire apical one-third of the septum, the left half of the middle third, and also crossed over to include a part of the anterior wall of the right ventricle. After the pathologic examination had been completed, the question arose as to whether the septal or right ventricular portion of the infarct was responsible for the Q wave in Lead $V_1$. Upon further reflection, it was evident that the Q wave could not have been due primarily to the right ventricular portion of the infarct, since activation of the septum in the usual fashion would have resulted in early positivity of the right ventricular cavity and thus an initial R wave in precordial leads over the right ventricle, irrespective of whether or not its free wall was infarcted. The pattern in Lead $V_1$ of this patient could be correlated with the distribution of the lesion in the middle third of the septum.

A small Q, small R, and deep S wave, with a normal QRS interval, were found in Leads $V_1$ and $V_2$ in Case 83, as a manifestation of an old healed infarct, practically confined to the apical half of the septum and distributed in patchy fashion between the two endocardial surfaces. This finding, together with a normal RS pattern in left ventricular Leads $V_3$ through $V_6$, led to an ante-mortem diagnosis of infarction localized to the interventricular septum.

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***A triphasic QRS complex, consisting of a Q, a late R, and a terminal S wave, may be observed in leads near the transitional zone in right bundle branch block due to septal infarction, as exemplified by Lead $V_2$ in Case 75. This and other comparable cases have been classified separately and discussed previously and therefore will receive no further consideration.**

Before a triphasic QRS complex with an initial Q wave in Lead $V_1$ and/or $V_2$ is attributed to septal infarction, other possible causes must be considered and excluded in the differential diagnosis. A pattern conforming to this general description may be found as a manifestation of uncomplicated left bundle branch block, right ventricular hypertrophy, and infarction of the free anterior wall of the left ventricle accompanied by displacement of the transitional zone to the right.

In left bundle branch block, irrespective of the presence or absence of septal infarction, right ventricular Leads $V_1$ and $V_2$ may display a Q wave, representing initial negativity of the right ventricular cavity due to reversal in the vector associated with septal activation; a minute R wave produced by passage of the impulse through the subjacent free wall of the right ventricle; and a final deep, broad S wave, reflecting negative potentials transmitted from the left ventricular cavity. Activation of the free wall of the right ventricle, in some cases of uncomplicated left bundle branch block, gives rise to a notch or mere slurring near the beginning of the downstroke of the fused Q and S deflections in these leads. Thus, in cases of left bundle branch block, the presence or absence of septal infarction cannot be determined from the contour of the QRS complex in right ventricular leads.

In uncomplicated right ventricular dilatation and hypertrophy, leads near the transitional zone may display a triphasic QRS complex, beginning with a small Q wave. The transitional zone is often broad in right ventricular dilatation and hypertrophy and may be displaced sufficiently to the right to include Positions $V_1$ and $V_2$, as exemplified by the triphasic QRS complex recorded in these leads as a manifestation of uncomplicated right ventricular dilatation and hypertrophy in Case 19 of a previous communication.[26] The differentiation of such patterns from those due to septal infarction is facilitated by additional leads below and to the right of the customary positions, namely, Leads $V_E$ and $V_{3R}$. The diagnosis of right ventricular hypertrophy can usually be established by the demonstration of a relatively large R wave and a late intrinsicoid deflection in leads to the right of the transitional zone, with or without a minute Q wave and a relatively small terminal S wave.

Abnormal QRS complexes might be recorded in Lead $V_2$, or even in $V_1$, as a manifestation of infarction of the free anterior wall of the left ventricle, if the transitional zone is displaced far to the right. This possibility could be excluded in Cases 50, 66, 83, and 152 by the presence of diphasic P waves, or upright P waves with steep terminal phase in Leads $V_1$ and $V_2$, indicating that the electrode was in the vicinity of the right atrium and hence was well to the right of the transitional zone.

When the heart is in the horizontal position, the potential variations of the right side of the septum and posteroinferior wall of the right ventricle are transmitted to the left leg and abnormalities referable to septal infarction may be found in Lead $aV_F$. A triphasic QRS complex, consisting of a small Q wave, a small R wave, and a deep S wave, was recorded in Lead $aV_F$ in Cases 60, 101, and 102 and could be correlated with infarction of the posterior part of the septum demonstrated at autopsy. The small Q wave probably represented initial

negativity of the right ventricular cavity, as a result of activation of the preserved right side of the posterior portion of the septum by impulses distributed through the right Purkinje system, whereas the small R wave was probably due largely to activation of the remainder of the septum by impulses distributed through the left Purkinje system. Activation of the posterior wall of the right ventricle probably contributed little toward the R wave in these cases, since the infarct continued into this portion of the heart. On the other hand, the infarct of the posterior wall of the right ventricle could not have been primarily responsible for the Q wave in Lead $aV_F$, since activation of the septum in the normal fashion should have produced initial positivity of the right ventricular cavity and thus an R wave in Lead $aV_F$, irrespective of the presence or absence of infarction of the free wall of the right ventricle.

(b) *Monophasic QS complex in both Leads $V_1$ and $V_2$* was found in one patient with primary septal infarction (Case 84), in fifteen patients with septal continuation of a large anterolateral or anteroposterior infarction (Cases 24, 25, 26, 29, 30, 37, 39, 40, 41, 49, 51, 53, 59, 65, and 91), and in one patient with extension from posterior infarction (Case 89). The lesion involved the apical two-thirds or more of the septum in thirteen cases, the apical one-half in three, and was limited to the left side of the posterior part of the septum in Case 89. Enough of the septum had been destroyed in all patients except Case 89 to account for the QS complexes in Leads $V_1$ and $V_2$ by the assumption that negative left ventricular cavity potentials transmitted through the septal infarct to the right precordium exceeded positive potentials coming from activation of septal remnants together with the free wall of the right ventricle. Before such an explanation could be accepted, it was necessary to consider other possible causes for the registration of QS patterns in leads from the right side of the heart.

A QS complex in both Leads $V_1$ and $V_2$ is not, in itself, diagnostic of septal infarction, since it is found in uncomplicated left bundle branch block, in left ventricular hypertrophy, and even in occasional normal hearts.[27] Left bundle branch block is often manifested by a QS complex in right ventricular leads, for reasons already discussed, but was not responsible for that found in any of the foregoing seventeen cases. The registration of a QS complex in Leads $V_1$ and $V_2$ in normal subjects and in patients with left ventricular hypertrophy is favored by a cardiac rotation which brings the right atrium beneath the sternum, carries the left apex backward, and tilts the mitral orifice to the right and forward. Such a position facilitates transmission of left ventricular cavity potentials toward the right atrium and may lead to a QS complex in Leads $V_1$ and $V_2$ when the negative potentials reaching the precordium through the above route exceed the positive potentials coming from activation of the septum and free wall of the right ventricle.

The ante-mortem decision as to whether QS complexes in Leads $V_1$ and $V_2$ are the result of septal infarction or merely a normal variant depends upon (1) the level of the RS-T junction and the contour of the segment in Leads $V_1$ and $V_2$, and (2) the QRS pattern in leads to the right and left.

The former criterion may be useful during the acute stage of infarction, but is of little or no aid after healing. Upward displacement of the RS-T junc-

tion, together with upward concavity of the RS-T segment in Leads $V_1$ and $V_2$, is a common finding in left ventricular hypertrophy, but may also occur in association with infarction. The combination of abnormal elevation of the RS-T junction and upward convexity or straightening of the segment in Lead $V_1$ and/or $V_2$ in Cases 24, 25, 26, 30, and 53 pointed toward recent infarction and corresponded satisfactorily with the post-mortem findings. However, a comparable pattern in Cases 49 and 84 was traceable to digitalis action, rather than acute infarction. Thus, the evidence furnished by the RS-T pattern in Leads $V_1$ and $V_2$ is of limited value.

The presence of a normal initial R wave in Lead $V_{3R}$ indicates that a QS pattern in Leads $V_1$ and $V_2$ is the result of infarction and not a normal variant.[18] The abnormal Q waves demonstrated in leads farther to the left in sixteen cases (all except Case 89) constituted indirect evidence that the QS complexes in Leads $V_1$ and $V_2$ were also the result of infarction. The QS pattern in Leads $V_1$ through $V_3$ in Case 84 could be correlated with the pathologic demonstration of a large infarct practically limited to the septum. However, in the other fifteen cases, the question remained as to whether the QS pattern in Leads $V_1$ and $V_2$ was a manifestation of the septal or the anterior portion of the infarct.

The contour of the P wave in Leads $V_1$ and $V_2$ was utilized as an index of the position of the electrode in reference to the cardiac surface. The registration of a steep intrinsicoid downstroke in the P waves in Cases 26, 29, 30, 37, 39, 40, 41, 51, 53, 59, and 65 indicated that the electrode in precordial Positions 1 and 2 was in the vicinity of the right atrium and that the QS patterns were referable to infarction of the septum, rather than to that of the free anterior wall of the left ventricle. The presence of auricular circus movement in Cases 25 and 49 and of low voltage P waves in Cases 24 and 59 left the position of the electrode in reference to the cardiac surface in doubt and hence left the question open as to whether the QS complexes in Leads $V_1$ and $V_2$ were a manifestation of the septal or the anterior portion of the infarct. Because of the extreme rarity of the preponderant registration of the potential variations of the anterior wall of the left ventricle in Lead $V_1$, it is probable that the QS patterns in this lead in Cases 24, 25, 49, and 59 were likewise due to the septal portion of the infarct.

*A monophasic QS complex in Lead $V_2$ in association with an RS complex in Lead $V_1$* was found in eight cases of anterolateral infarction, which continued into the septum. An unequivocal diagnosis of infarction could be made from the findings in Lead $V_2$, together with the initial R wave in Lead $V_1$ and the abnormal Q waves in leads farther to the left. The diphasic P waves in Lead $V_2$ in Cases 33 and 57 and the upright P waves with steep terminal limb in Cases 27, 62, and 79 indicated that the electrode was in the vicinity of the right atrium and thus reflected the potential variations of the right side of the septum and right ventricle, rather than those of the anterior wall of the left ventricle. The QS complex in Lead $V_2$ in these five cases was therefore attributed to the septal, rather than the anterior, portion of the infarct. The contour of the P wave in Lead $V_2$ in Cases 32 and 52 indicated that the electrode lay beyond the right atrium, but gave no information as to whether it was over the right or left ventricle. The

major source of the ventricular complex in Lead $V_2$ was also indeterminate in Case 48 because of the presence of fine auricular fibrillation.

*Monophasic QS complex in right ventricular Lead $aV_F$ of a horizontally placed heart* may occur as a manifestation of septal infarction, of left bundle branch block, or as a normal variant. The QS complex in Lead $aV_F$ in Cases 85, 100, and 111 was believed referable to the septal infarct because of the abnormal slurring or notching and prolongation of the descending limb, and that in Case 53 was attributed to the acute septal infarct because of the accompanying RS-T pattern. More detailed discussion of the findings in Lead $aV_F$ will be reserved for a subsequent manuscript.

(c) *Abnormal displacement of the RS-T segment in Lead $V_1$ and/or $V_2$, suggesting recent infarction*, was found in association with a normal initial R wave in five cases of acute infarction of the septum and anterior wall of the left ventricle (Cases 23, 34, 61, 77, and 80) and in two cases of acute posteroseptal infarction (Cases 87 and 88). Although an epicarditis of the anterior wall of the right ventricle, secondary to extension of the pericarditis accompanying acute left ventricular infarction, is a possible cause for displacement of the RS-T segment in right ventricular leads, it was not responsible for the pattern in Leads $V_1$ and $V_2$ of any of these seven cases. The changes of the RS-T segment in Cases 87 and 88 were believed referable to the acute infarct of the posterior half of the septum and the initial R wave in Leads $V_1$ and $V_2$ was probably derived from the intact anterior half of the septum and free wall of the right ventricle. The RS-T changes in the other five cases could be correlated with the extensive acute infarct of the septum. The preservation of the R wave in Cases 77 and 23 could be explained by the fact that the tracings were obtained only four and twelve hours, respectively, after the onset of symptoms. The large septal lesion in the other three cases should have permitted transmission of negative left ventricular cavity potentials to the right precordium sufficient to counterbalance the positive potentials coming from activation of septal remnants and the free wall of the right ventricle and thus should have led to an initial Q wave in Leads $V_1$ and $V_2$. The registration of an initial R wave in these leads was probably due to a marked reduction in opposing left ventricular cavity potentials secondary to extensive infarction of the free wall of the left ventricle.

5. *Absence of Direct Evidence of Septal Infarction.*—The findings in leads facing the right side of the septum and epicardial surface of the right ventricle (precordial leads to the right of the transitional zone and, in addition, Lead $aV_F$ in horizontally placed hearts) that constitute direct evidence of septal infarction have been discussed at length. In brief summary, these findings are: (1) right bundle branch block, characterized by an abnormal Q wave and/or a classical RS-T pattern; (2) a triphasic QRS, consisting of a small Q wave, a small R wave, and a deep S wave and occurring in the absence of right ventricular hypertrophy; (3) abnormal QS pattern accompanied either by a normal R wave in leads farther to the right or by abnormal Q waves in leads farther to the left. The findings in the same leads which may be regarded as suggestive of septal infarction are: (1) incomplete patterns fulfilling part, but not all, of the criteria in one of the three

foregoing categories; (2) classical displacement of the RS-T segment in Leads $V_1$ and $V_2$ without QRS abnormalities in these leads, but accompanied by abnormal Q waves in leads farther to the left. The combination of left bundle branch block and abnormal Q waves in left ventricular leads is also diagnostic of septal infarction, but could not be established definitely in any case in this series.

An analysis of the electrocardiograms of the six patients with pathologically demonstrated primary septal infarction revealed diagnostic evidence in four, consisting of classical right bundle branch block patterns in three and triphasic QRS in one; a strongly suggestive QS pattern in right precordial leads of one patient; and a QS pattern in right ventricular Lead $aV_F$ compatible with septal infarction in one patient.

The septal extension of a large anterior or anteroposterior infarction was manifested by diagnostic electrocardiographic signs in twenty-nine cases, by suggestive signs in eleven, and by no direct evidence in the other nineteen cases. In nine of the latter group, leads from the precordium and left leg revealed signs of anteroposterior infarction. Since large anterior infarcts that continue into the posterior wall of the left ventricle almost invariably extend through the septum, electrocardiographic signs of an anteroposterior lesion constitute indirect evidence, presumptive of infarction of the intervening septum.[17] However, indirect evidence of this type cannot be regarded as diagnostic of septal infarction, since signs of involvement of the anterior and posterior walls may result from two separate lesions, neither of which extends into the septum, as in Case 68.

In analyzing the causes of diagnostic failure in the foregoing nineteen cases, it is noteworthy that no direct electrocardiographic evidence of septal infarction was found in any of the six patients in whom the septal extension was confined to the apical one-third (Cases 22, 42, 43, 64, 67, and 96). Since infarction of the apical one-half of the septum was detected electrocardiographically in eight of thirteen patients, it would appear that a lesion approaching this size represents the minimum necessary for diagnostic signs. However, direct electrocardiographic evidence of septal infarction was absent, not only in five patients with involvement of the apical half (Cases 46, 56, 58, 63, and 81), but also in eight patients with involvement of the apical two-thirds or more (Cases 31, 35, 36, 38, 47, 55, 82, and 151), including one patient with a large perforation (Case 55). Left bundle branch block was present in Cases 81 and 82, but the patterns were not diagnostic of septal infarction in either instance, even though the conduction defect was probably secondary to the septal lesion in the former. The absence of direct electrocardiographic evidence in Cases 36 and 38 was attributable to a very recent septal lesion of insufficient duration to obliterate the response to the activating impulse. The registration of initial R instead of Q waves in right ventricular leads of the remaining nine patients was considered an indirect effect of the extensive infarct of the free wall of the left ventricle. As a result of the latter, the negative potentials referred to the left ventricular cavity and thence through the septal infarct toward the right precordium were probably so reduced that they failed to counterbalance positive potentials coming from activation of the free wall of the right ventricle and from intact remnants of septum. Right

ventricular hypertrophy in Case 47 was an additional factor that contributed directly toward the initial upstroke recorded in Leads $V_1$ and $V_2$.

Septal extension of posterior infarction was indicated by the association of complete A-V block with signs of recent posterior infarction in Cases 88 and 104, but was manifested by abnormalities in the ventricular complex of Lead $V_1$ in only two of the twenty-four patients (Cases 87 and 88). These consisted of dome-like elevation of the RS-T segment in both cases and terminal right bundle branch block in the former. The rarity of QRS abnormalities in right precordial leads was attributable to the fact that septal extensions from posterior infarction were almost invariably confined to the posterior one-third to one-half of the septum. On the other hand, QRS abnormalities referable to infarction of this portion of the septum were recorded in Lead $aV_F$ in Cases 60, 100, 101, 102, and 111 as a result of horizontal position of the heart. Thus, electrocardiographic signs indicative of extension of a posterior infarct into the septum were found in only eight of the twenty-four patients. Bundle branch block was found in four additional patients, but was considered independent of the septal infarct. The remaining twelve patients displayed no evidence suspicious of the septal lesion.

*Infarction of the right ventricle* was not encountered as an isolated finding in any of the 161 cases. The closest approach was in a patient (Case 124) who was admitted with an acute infarct of the posterolateral wall of the left ventricle and five weeks later had a second attack, characterized by infarction of the entire apex of the right ventricle, the adjoining septum, and a small segment of the posteroseptal wall of the left ventricle. An electrocardiogram made two hours after the second attack showed no change in the QRS pattern, but displayed increased upward bowing of the RS-T segment in Lead $aV_F$ and reciprocal RS-T depression in Leads $V_3$ through $V_6$ and in Lead $aV_L$. These changes were indistinguishable from those produced by acute infarction limited to the posteroseptal wall of the left ventricle. Continuation of an infarct of the posterior wall of the left ventricle across the septum into the posterior wall of the right ventricle was demonstrated pathologically in twelve other patients (Cases 35, 38, 52, 60, 87, 88, 90, 100, 101, 102, 104, and 114), but was not manifested by electrocardiographic signs distinctive of the right ventricular lesion in any case. Extension of an infarct of the anterior wall of the left ventricle across the septum into the anterior wall of the right ventricle was demonstrated pathologically in six patients (Cases 11, 50, 54, 71, 72, and 79), but was not manifested by distinctive electrocardiographic signs, except, perhaps, in Case 71. The marked elevation of the RS-T junction in right ventricular leads in this case may have been due, in part, to acute injury to the anterior wall of the right ventricle.

## SUMMARY

Infarction of the interventricular septum was demonstrated pathologically in 102 cases, which represents an incidence of 63 per cent in a series of 161 cases. The findings in thirteen cases of localized anteroseptal infarction were analyzed in a previous report. The present study is concerned with a correlation of electrocardiographic and pathologic findings referable to the septal lesion in the remain-

ing eighty-nine cases. These cases were classified into three groups, according to the distribution of the lesion at autopsy: Group A, infarction primarily in and largely confined to the septum in six cases; Group B, septal extension of large anterior or anteroposterior infarction in fifty-nine cases; Group C, septal extension of posterior infarction in twenty-four cases.

The following electrocardiographic patterns could be correlated directly with the septal infarct found at autopsy:

1. Complete A-V block was observed as a manifestation of extension of an acute posterior infarct into the base of the septum in two cases.

2. A QRS interval of 0.12 second or more, a prominent late R wave, and a delayed intrinsicoid deflection in leads from the right precordium were found in fourteen cases and were attributable to septal infarction in thirteen of the group because of the presence of a distinct Q wave and/or abnormally elevated RS-T junction in these leads. The infarct was confined to the apical one-half to two-thirds of the septum in five of the cases and probably caused delay in right ventricular activation by interruption of conduction through the right Purkinje system, rather than the right bundle branch. Since the electrocardiographic findings in these cases were similar to those in other cases with infarction reaching the anatomic site of the bundle of His, the customary term, "right bundle branch block," was retained to designate the conduction defect. The abnormal Q wave in right ventricular leads constituted the chief distinguishing feature from uncomplicated right bundle branch block and was recorded because of the preponderance of negative potentials transmitted from the left ventricular cavity through the infarcted septum to the right precordium over reduced positive potentials coming from activation of intact remnants of septum. The differentiation of infarcts limited to the septum from those continuing into the anterior wall of the left ventricle depended upon the QRS pattern in leads to the left of the transitional zone and was rendered difficult in three of the cases of right bundle branch block by displacement of the transitional zone into the left axilla. The recognition of extension of a septal infarct into the posterior wall of the left ventricle was possible from Lead $aV_F$ in intermediate to vertical cardiac position, but not in transversely placed hearts, since reference of the potential variations of the right side of the septum to the left leg, as a result of horizontal position, produced patterns in Leads $aV_F$, II, and III which simulated those caused by posterior infarction. The standard limb leads did not reveal diagnostic evidence of septal infarction in any of the thirteen cases.

3. A QRS interval of 0.12 second or more, an initial upstroke in all leads facing the left ventricle, and an abnormally delayed intrinsicoid deflection in left axillary leads were found in four cases and were attributed to left bundle branch block independent of the septal infarct in three of these. In the remaining case, autopsy revealed an acute infarct limited to the left side of the apical two-thirds of the septum and the subendocardial layer of the anterior and posterior walls of the left ventricle, and the pattern was attributed to septal activation by impulses distributed through the right Purkinje plexus.

4. Patterns characterized by a QRS interval of 0.12 second or more, an initial Q wave, and a late intrinsicoid deflection in precordial leads over the left

ventricle were found in ten cases and were definitely attributable in three of these to an infarct of the free wall that was dense in the subendocardial layer and patchy in the more superficial portion of the myocardium. This explanation was favored in the other seven cases, but the alternative possibility of left bundle branch block due to extensive septal infarction could not be positively excluded.

5. A triphasic QRS complex of normal duration, characterized by a small Q wave, a small R wave, and a deep S wave, was found in right ventricular Leads $V_1$ and/or $V_2$ in four cases and was well correlated with the distribution of the septal infarct at autopsy. These findings may be considered diagnostic of septal infarction, provided right ventricular hypertrophy can be excluded. A similar pattern was found in Lead $aV_F$ in three other cases and could be correlated with infarction of the posterior part of the septum. The potential variations of the right side of the septum were transmitted to the left leg in these cases because of horizontal position of the heart.

6. A monophasic QS complex of normal duration, found in Leads $V_1$ and $V_2$ or in $V_2$ in twenty-four cases, was regarded as a manifestation of infarction, rather than as a normal variant, because of the presence of one or more of the following findings: an abnormal upward displacement of the associated RS-T segment, a normal initial R wave in leads farther to the right, or abnormal Q waves in leads farther to the left. The abnormal QS complexes in Leads $V_1$ and $V_2$ in most of the cases were attributable to infarction of the septum, rather than infarction of the free anterior wall of the left ventricle, because of the presence of an intrinsicoid deflection in the accompanying P wave, indicating that the electrode was in the vicinity of the right atrium and thus faced the right side of the septum and right ventricle. The replacement of the initial R wave by a QS complex could be correlated with septal infarction that permitted transmission of left ventricular cavity potentials to the right precordium. An abnormal QS deflection in Lead $aV_F$, found in four patients with horizontally placed hearts, was believed referable to septal infarction.

7. Abnormal RS-T displacement, consistent with recent infarction, was found in right ventricular Leads $V_1$ and/or $V_2$ in association with normal initial R waves in seven cases. This finding could only be regarded as suggestive of septal infarction during life, but was believed referable to the recent septal infarct found at autopsy in each case.

Diagnostic or suggestive evidence of septal infarction was found in all six cases of primary septal infarction. Direct electrocardiographic evidence of the septal lesion was absent in sixteen of the twenty-four cases of septal extensions from posterior infarction, principally because of limitation of the lesion to the posterior one-third to one-half of the septum; and absent in nineteen of the fifty-nine cases of septal extension from anterior or anteroposterior infarction. The diagnostic failures were attributable to limitation of the infarct to the apical one-third of the septum in six of the latter group, to left bundle branch block in two, to a very recent septal lesion in two, and, in the remainder, to marked reduction in opposing negative potentials transmitted to the right precordium as a result of extensive infarction of the free wall of the left ventricle. In nine of the nineteen cases without direct electrocardiographic evidence of septal infarc-

tion, leads from the precordium and left leg revealed signs of anteroposterior infarction, which could be regarded as indirect evidence, presumptive of the presence of infarction in the intervening septum.

Isolated right ventricular infarction was not found in any case. Left ventricular infarcts continued across the septum into the posterior wall of the right ventricle in thirteen cases and into the anterior wall of the right ventricle in six others, but were not manifested by electrocardiographic signs distinctive of the right ventricular involvement in any case.

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# A METHOD FOR RECORDING THE ARTERIAL PRESSURE PULSE AND BLOOD PRESSURE IN MAN

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THE ability to record accurately and to have immediately available tracings of arterial pressure pulses should be of value to the investigator and the clinician. Methods in current use for recording arterial pulse waves involve maintenance of a rigid needle in an artery, a requisite which limits the conditions under which pulse contours can be obtained. They also require the development of photographic paper before a tracing can be analyzed.

We propose to present a method for the continuous recording of pulse waves and blood pressure in man which has certain practical advantages over the techniques previously described. A small plastic catheter, inserted into an artery through a needle, is left in the artery when the needle is withdrawn. Attached to a capacitance manometer, this technique permits recording for long periods of time without discomfort and allows relatively free mobility of the subject. The record, received by an ink-writing oscillograph, permits continuous knowledge of blood pressure and provides an opportunity for observation of any changes in the contour of the pulse wave which may develop. The apparatus is compact, mobile, and flexible.

By comparing the contour of the pulse waves in the same subject under different conditions, one can obtain information concerning changes in stroke volume, vasoconstriction, or distensibility of the arterial system. Interpretations of this type will be illustrated by tracings obtained from a series of 100 patients studied to date.

## METHOD

Accurate recording of pressure changes depends among other things on the selection of tubing of proper length and cross-sectional area. A small catheter is desirable from the standpoint of comfort, end pressure, turbulence, and capacity. The last must be considered since the smaller the capacity for a given length, the smaller will be the volume pressure changes with bending. Also the effective mass of fluid is reduced. Lead tubing has been used by others to secure flexibility between the artery and manometer and by comparison the effective mass of the latter becomes much larger. With underdamped systems of low natural frequency this factor becomes important in the possible produc-

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tion of overshoot. We use the Lilly capacitance manometer[1] which has a volume displacement of $10^{-6}$ ml. per 100 mm. Hg, thus permitting the use of small catheters.[2] This manometer is critically damped to 100 cyles per second.

The plastic catheters used in our apparatus are made from a synthetic polyvinyl resin.* The tubing as received from the manufacturers is quite flexible and elastic since it is intended for such application as electrical insulation. The flexibility is the desirable feature. The elasticity must be reduced to such a degree that it does not introduce a damping factor in the cardiovascular pressure ranges. This is accomplished by heating the plastic in an oven for seventy-two hours at 110° centigrade. Since the plastic is thermosetting, the tubing can, at the same time, be drawn out and set to any desirable length and diameter. The lower right insert in Fig. 1 pictures the device for drawing out this tubing. The entire device and tubing is placed in the oven. The catheters are drawn out to an outside diameter of about 0.45 mm. and an inside diameter of about 0.21 millimeter. At the end of the heating period they are cut into 12.0 cm. lengths with a sharp, nonhollow ground razor blade and stored in 1:1000 Zephiran chloride solution.

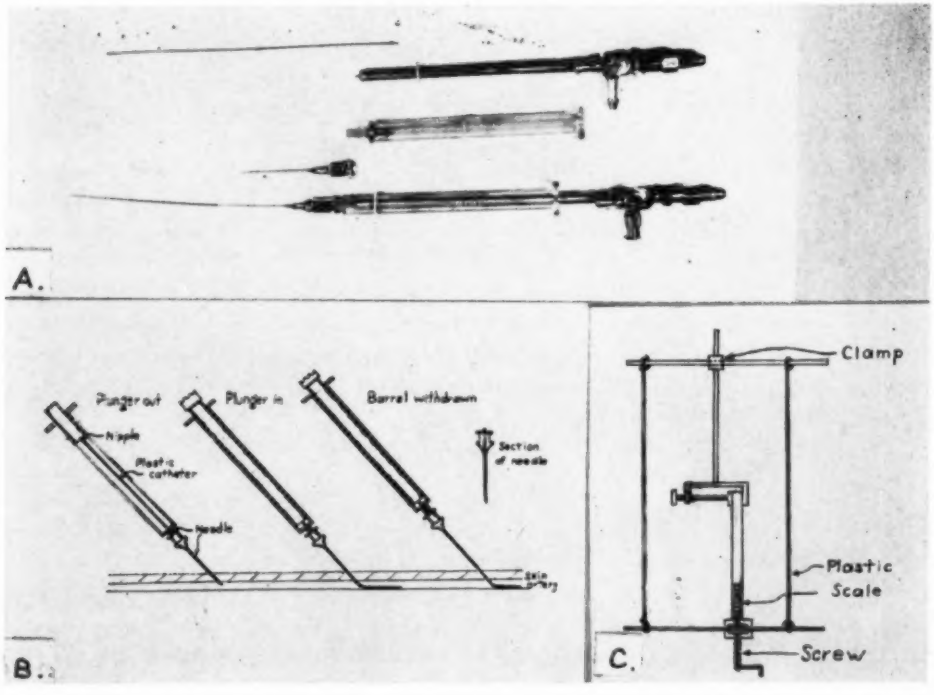


Fig. 1.—*A*, From above downward. Catheter, plunger, syringe, needle, and assembled device. *B*, Method of catheterizing. From left to right: arterial puncture made with plunger elevated, catheter injected into artery by pushing plunger down, entire device pulled back thus pulling needle out of tissue. Insert shows steel tubing projecting into hub of needle. *C*, Adjustable rack for stretching plastic tubes a known distance and for maintaining this degree of stretch during baking.

*Manufactured by the Irvington Varnish and Insulator Company, Irvington, N. J.

The catheterization device consists of a hollow steel plunger ground to fit a standard 1.0 c.c. tuberculin syringe. At one end is soldered a nipple upon which the catheter fits. The other end is fitted to the manometer. The arrangement is shown in the upper insert in Fig. 1. The method of catheterization is drawn schematically in Fig. 1, also. The barrel of the syringe is filled with sterile physiologic saline. The arterial puncture is made; the plunger is then projected downward, thus injecting the catheter into the vessel. The needle is then withdrawn from the skin leaving only a flexible tube within tissue. It has been found highly practical to secure special steel needles with a thinner than usual wall and thus to preserve valuable inside diameter. For example, the standard 22-gauge needle has an outside diameter of about 0.7 mm. and an inside diameter of about 0.4 millimeter. We are using 22-gauge needles with an inside diameter of 0.58 millimeter. Thus, the catheter diameter may be increased by 0.18 millimeters. The same principle may be utilized in making more innocuous the use of larger diameter catheters for manometers of larger displacement or for using longer catheters where the diameter must be increased for any given displacement.

The ink-writer-amplifier couple* is capable of following, with linear response, changes from direct current to over 100 per second. The oscillograph is made up of a powerful D'Arsonval moving coil galvanometer to which is attached a writing arm and pen. The input voltage range is from 0.001 to 200 volts with an input impedance of 10.0 megohms. The operating voltage is from 95 to 125 volts at 60 cycles per second. The width of the recording paper is 50.0 mm., but to insure accurate knowledge of base line shifts, the base is kept at the 5.0 mm. level. Amplification can be changed easily and rapidly to allow use of maximal sensitivity for any blood pressure whether at hypotensive or hypertensive levels. Normally a sensitivity of about 3.0 to 4.0 mm. Hg per millimeter of deflection is adequate. The paper is driven by a synchronous motor with gears allowing readily changed speeds of 5, 25, and 125 mm. per second. Notations can be made on the paper as the record is being traced.

The position of the base line may be determined at will by turning the stopcock shown in Fig. 3 to such a position that the diaphragm is exposed to the atmosphere. Sensitivity may be checked at will by exposing the back of the membrane to a known air pressure. An electrically analogous situation exists in the calibration of an electrocardiograph. The tube conveying this pressure is shown in Fig. 2.

After assembly, but before catheterization, the manometric system is flushed with a boiled 6 per cent sodium citrate solution. Saline and heparin may also be used. This is done by filling a pressure reservoir which is attached to the manometer via a side tube and needle valve. The pressure reservoir consists of a 50 to 100 c.c. syringe and plunger in a case, the latter being filled with air under pressure. An easy method of determining whether or not the system has been freed of air consists in adjusting the needle valve so that a trickle of solution is flowing from the end of the catheter. A finger or other surface then occludes

*Supplied by the Brush Development Company, Cleveland, Ohio.

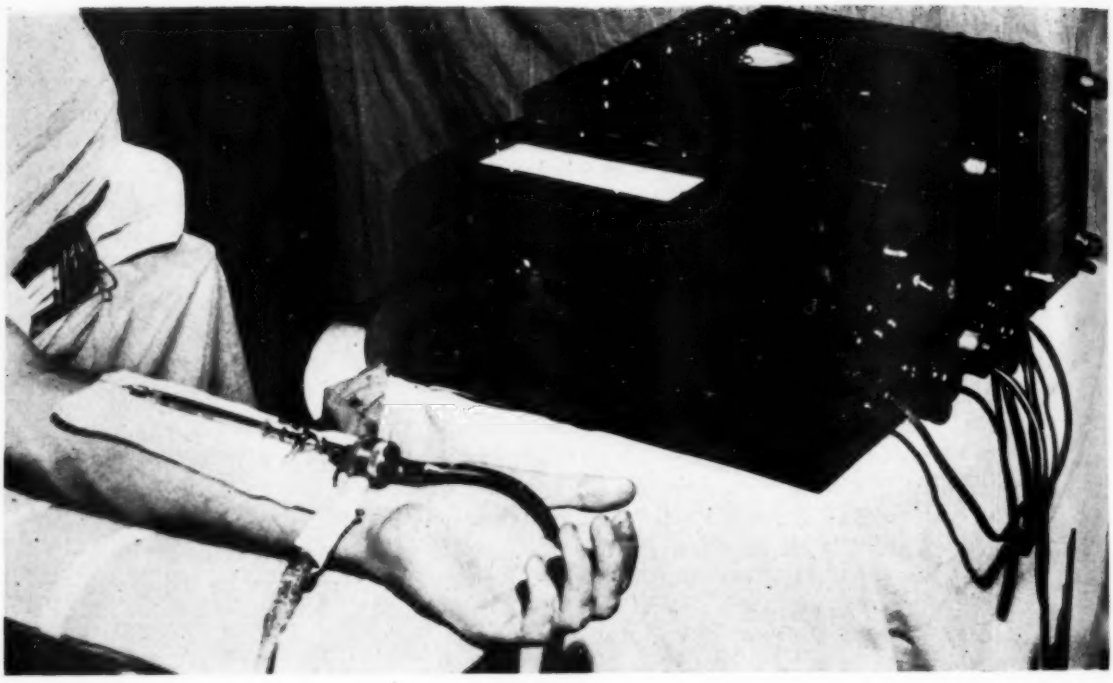

Fig. 2.—A photograph to show the recording equipment, pick-up unit, and catheter. On the far right is seen the direct current amplifier and ink-writer. Not shown is the Lilly amplifier, calibration device, and fluid reservoir. The calibration tube is seen passing over the palm. Electrical lead and fluid tube can be seen entering the pick-up at right angles. Syringe barrel is seen attached to the pick-up through a three-way valve. The catheter is seen projecting from the needle and into the arm.

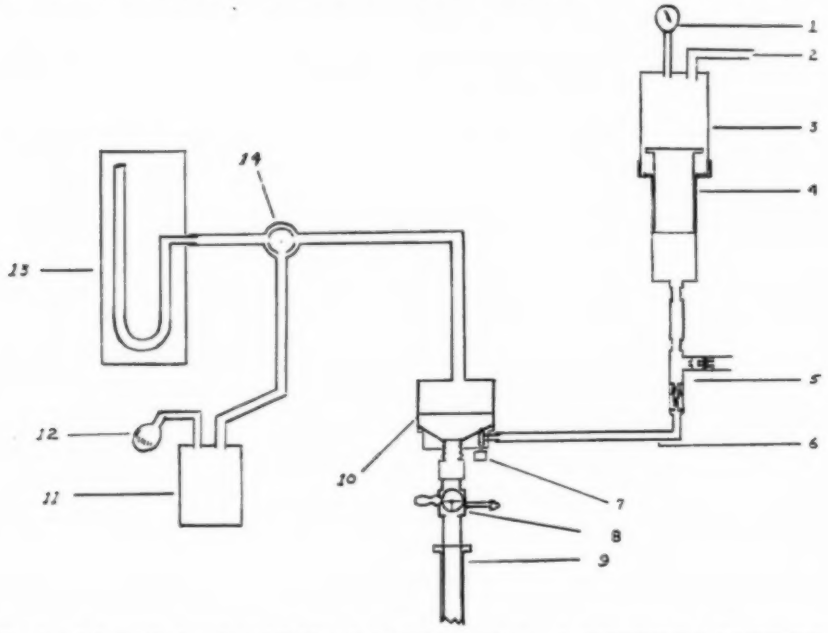


Fig. 3.—Schematic drawing of fluid and calibrating system. *1*, manometer; *2*, air pressure at about ten pounds per square inch; *3*, jacket around syringe; *4*, syringe and plunger; *5*, two-way B-D valve for filling; *6*, plastic tube to pick-up; *7*, needle valve for controlling flush; *8*, three-way B-D valve for recording base line; *9*, plunger for catheterization syringe; *10*, manometer diaphragm; *11*, calibration air pressure reservoir pumped up with *12*; *13*, mercury manometer for reading calibration pressure; *14*, three-way B-D valve for exposing the back of the membrane (*10*) to either atmospheric pressure or calibration pressure.

the end so that the pressure rises in the manometer. Sudden release of the occlusion reduces the pressure and gives an accurate enough recording of the relaxation time so that the presence of air is obvious. Fig. 4,*A* demonstrates such a test. The three curves on the left demonstrate the presence of air. During the recording time, the citrate reservoir under pressure remains attached to the manometer. Since most valves under pressure leak somewhat (1.0 ml. or less per hour) this insures that any leakage will be in the proper direction and that changes in blood pressure will not cause clotting. This does not affect significantly the pressure level or pulse curve. Sensitivity and base line calibrations are also made under the same circumstances.

The time relationships of the over-all response of the system are slightly longer than at critical damping. An interval of about 0.014 second is required

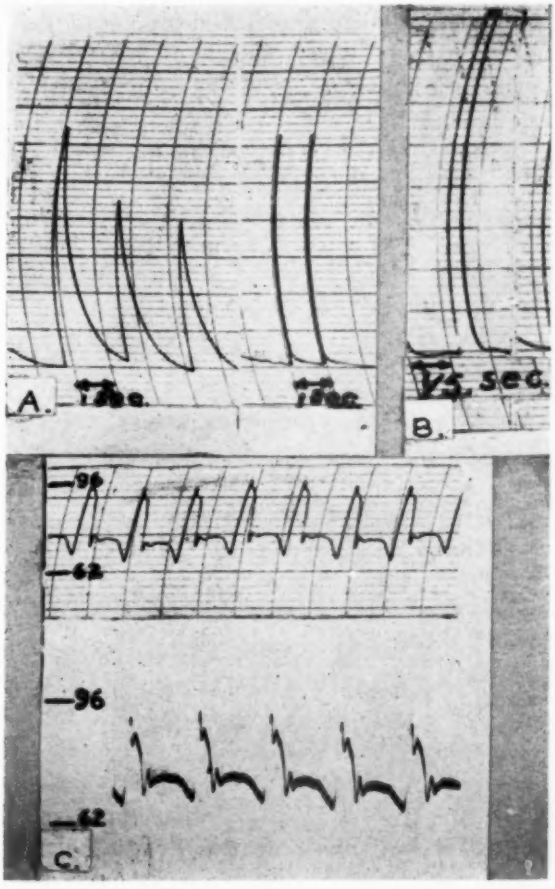


Fig. 4.—*A*, Left three curves demonstrate the presence of air. The right two, after the air has been flushed out. Paper speed, 5 mm. per second.

*B*, Same procedure at 25 mm. per second.

*C*, Comparison of ink-writer and camera records. The upper curve is recorded by the ink-writer. The lower is recorded photographically from a Kipp and Zonnen galvanometer critically damped with a period of 0.01 second. These are simultaneous curves through the same catheter in the aorta of a dog 1.0 cm. from the aortic valves.

for 90 per cent relaxation by the method of Lilly.[3] It is felt that in the study of an unknown pressure pulse such an overdamped system eliminates the possibility of overshoot, provided the frequency response is the same as or faster than that of the unknown pressure pulse.

One hundred patients have been catheterized to date as described. The only discomfort is during the initial puncture. Visual recording provides immediate information that the artery has been entered; hence, arterial puncture is greatly facilitated. This fact and the practicability of a small bore needle reduces the initial discomfort to such a degree that no local anesthesia is necessary. The small size of the needle and catheter has sharply reduced the likelihood of hematoma formation. After withdrawal of the needle the presence of the catheter itself in the artery causes no sensation. Some of these patients have been followed continuously through the induction of anesthesia, during surgery, and in the postoperative period. Others have been studied under controlled physiological stresses. They ranged in age from 6 to 79 years and represented a wide variety of cardiorespiratory abnormalities. The environmental temperature during this study varied from 70 to 96° Fahrenheit.

It should be stressed that care must be exercised in avoiding occlusion of the artery from which the tracings are made. Errors in interpretation of records from the brachial artery, for example, might be serious if one overlooked occlusion of this vessel as the result of arm movements or from lying on the arm.[12] In addition, local effects in the circulatory bed of the vessel could cause erroneous assumptions of changes in the general circulation.

## RESULTS

No attempt has been made to study thoroughly one particular type of circulatory disease. Nor has the action of any single drug or procedure been specifically analyzed. Experiments along these lines are being carried on at present. This report is designed to describe the method and to illustrate the utility of the apparatus in the recognition of imbalance of the circulation produced by changes in peripheral resistance, stroke volume, or distension of the vascular system.

1. *Peripheral Resistance.*—Fig. 5 demonstrates one sequence of events noted after the administration of a spinal anesthetic. This record is from a man, 72 years of age, who was scheduled for a suprapubic prostatectomy. The first tracing (7:45) is the preanesthetic pulse wave as recorded from the brachial artery. The second tracing (8:06) shows that a decided change has occurred in the circulatory system, yet systolic and diastolic levels have not altered greatly. Palpation and sphygmomanometric pressure measurements did not indicate the character or magnitude of the shift. This change is interpreted to mean predominantly a reduction in peripheral resistance and is similar to that reported by Volpitto and associates.[4] There is a rapid fall in the predicrotic limb of the pulse and the pressure has approached or reached diastolic levels before the incisura has appeared. Our experience indicates that with this change the general pressure levels may be maintained, provided no additional stress is

placed on the individual. The avoidance of additional stress is accomplished usually by seeing that the patient lies quietly and is undisturbed. Sometimes surprisingly small stimuli will cause a distinct decrease in blood pressure. In this case the skin incision, of which the patient was unaware, was followed by a reduction of about 25 mm. Hg in the systolic pressure.

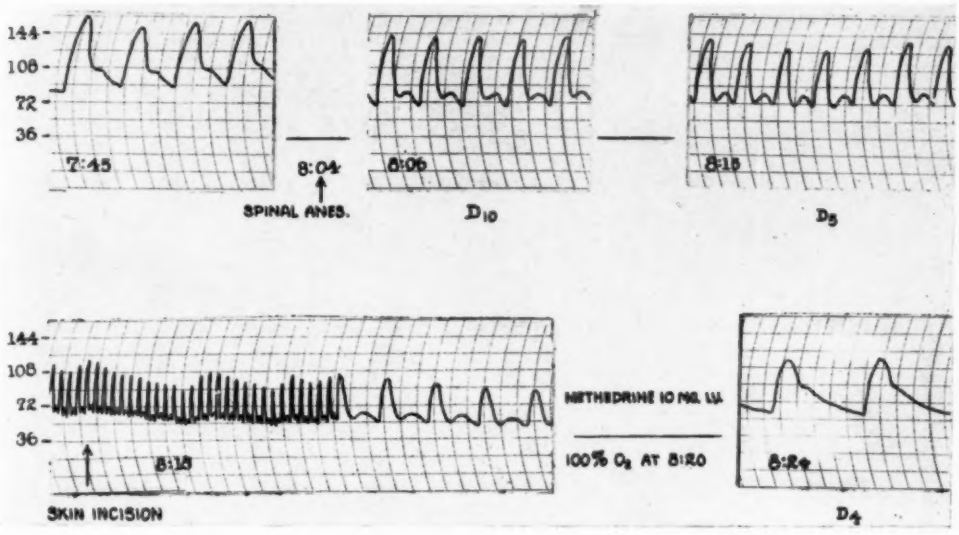


Fig. 5.—Pluse tracings from the brachial artery of a 72-year-old man.

7:45: Preanesthetic pulse wave. 8:04: Pontocaine Hydrochloride, 12.0 mg., given subdurally; no pressor drug given prior to induction. 8:06: Abolition of sensation to pin prick to the tenth dorsal dermatome (D-10). 8:14: Patient wheeled into operating room. 8:15: Abolition of sensation to D-5. Patient still lying quietly and undisturbed.

8:18: Methedrine, 10.0 mg., given intravenously; 100 per cent oxygen administered. 8:24: Abolition of sensation to D-4. Pressure pulse alteration due to administration of vasopressor drug and oxygen.

These records were traced with green ink on a red background; hence, they have been retraced for reproduction. Original line 0.1 mm. thick. Waviness of the lines are artifacts due to this retracing.

Horizontal lines equal 1.0 mm.; vertical lines equal 5.0 mm.; paper speed 25 mm. per second except first part of 8:18 tracing which is 5.0 mm. per second. Pressure scale on left margin in millimeters of mercury.

2. *Stroke Volume.*—Fig. 6 demonstrates a second cardiovascular change associated with spinal anesthesia. There is a hypodynamic rounded systole, in contrast to the sharp, unsustained pulse where the incisura approaches diastolic levels as seen in the previous figure. The postanesthetic pulse (9:20) is interpreted as representing a change primarily due to a reduced stroke volume and is similar to that reported by Wiggers.[5] The pulse is not collapsing and has no rapid fall of the predicrotic limb. With this alteration the pressure level cannot be maintained and will steadily fall despite the degree of quiescence of the patient.

Fig. 7 represents a case in which both of the changes previously mentioned occurred. This record was obtained from a woman undergoing a surgical procedure designed to remove a portion of the right lobe of the liver. The second tracing (8:01) demonstrates a change due to predominant reduction in peripheral resistance which followed the anesthetic. During the operation a tourniquet was

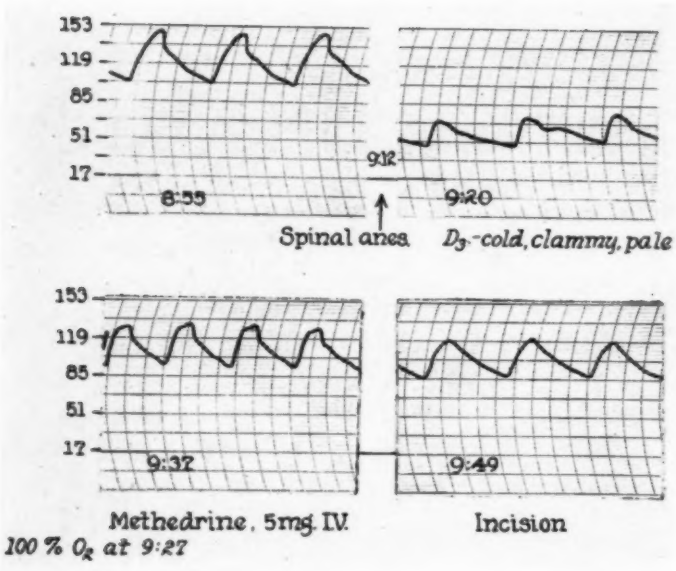


Fig. 6.—Brachial artery tracings from a 55-year-old man about to undergo an operation for bilateral inguinal herniorrhaphy. 8:55: Preanesthetic pulse tracing. 9:12: Pontocaine hydrochloride, 14 mg., given subdurally. No pressor drug given. 9:20: Postanesthetic tracing. The pressure levels fell concurrently with the formation of this type of pulse pattern. Abolition of pin prick sensation to D-4. Skin was pale, clammy, and cold.

9:27: Methedrine, 5.0 mg., administered intravenously. 9:36: Patient wheeled into operating room. 9:37: Pressure pulse ten minutes after administration of vasopressor drug. 9:49: Skin incision made. The pressure wave again assumed the character of the 9:20 figure and the pressure gradually fell as the vasopressor drug wore off.

Paper speed in all sections is 25 mm. per second. Pressure levels indicated at left margin.

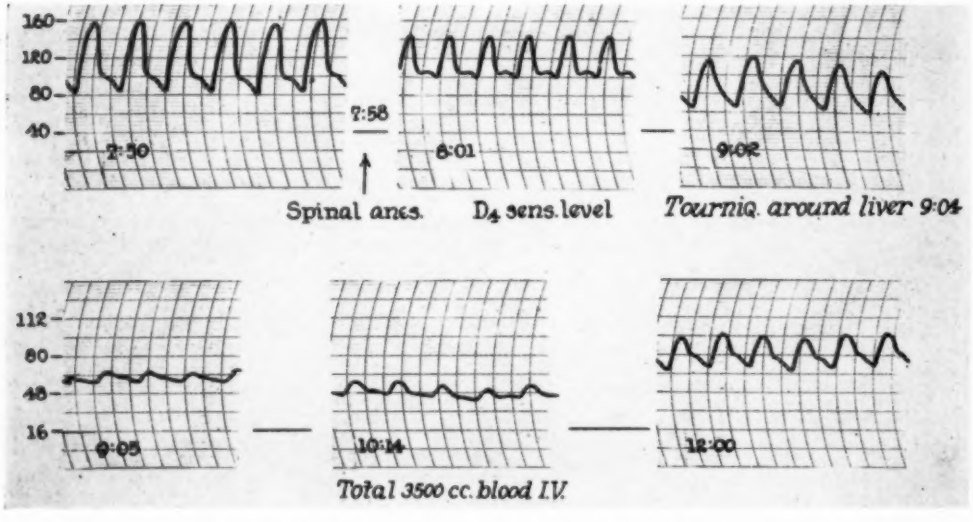


Fig. 7.—Brachial artery tracings from a 45-year-old woman about to undergo operation for partial removal of the liver. 7:50: Preanesthetic pulse. This patient had an oral temperature of 101.5° F. and was receiving chemotherapy and penicillin preoperatively. 7:58: Pontocaine hydrochloride, 12.0 mg., given subdurally. No pressor drug. 8:01: The base line in this section is at the bottom of the paper, whereas the base line of all other tracings is 5.0 mm. from the bottom. The same scale of pressure holds for the upper three tracings. Thus, the diastolic pressure is 80 mm. Hg and the systolic pressure is 124 mm. of mercury. Abolition of pin prick sensation at D-4.

8:05: Patient wheeled into operating room. 9:02: Prior to this tracing the pressure level had fallen and Methedrine had been given. 9:04: Tourniquet placed around liver and tightened thirty seconds later. The pressure fell from 130 systolic and 100 diastolic to that seen in the 9:05 tracings. 10:14: 3,500 c.c. blood had been given intravenously. 12:00: End of operation.

placed around the liver and tightened. In so doing, venous return was reduced as the result of occlusion of the inferior vena cava. There was a rapid fall in mean and pulse pressures, yet the pulse was full to the extent that the dicrotic limb did not drop rapidly. Removal of the tourniquet was followed by a rise in the blood pressure.

3. *Hemorrhagic Underdistention.*—Fig. 8 demonstrates a case in which the pulmonary vein was inadvertently cut with excessive hemorrhage. Here the mean and pulse pressures were low but with an unsustained type of pulse. There is a distinct difference in the character of this sort of underdistention and of that seen in Fig. 6, although both show approximately the same pulse rate and general pressure levels. Thus, underdistention due to hemorrhage could be distinguished from that of the previous example of reduced stroke volume under these conditions. Despite heroic transfusion therapy, this patient died on the operating table. There are other circulatory conditions which conceivably might produce similar curves. However, examination and previous control curves on the same patient will reduce this possibility to insignificance.

Fig. 9 is a series from the record obtained on a 42-year-old man with hypertension who had been subjected to a bilateral thoracolumbar sympathectomy and splanchnicectomy (approximately D-6 to L-3 inclusive) four months prior to this time. The patient was brought into the hospital for a study of the circulatory changes produced by such an operation. Included in this evaluation were simultaneous estimations of cerebral blood flow by the method of Kety and Schmidt[6] and of cardiac output by the ballistocardiogram.[7] Differential spinal anesthesia was produced as described by Sarnoff and Arrowwood.[8] This latter technique involves the subarachnoid injection of very dilute (0.2 per cent) concentrations of procaine in an attempt to block the small, relatively thinly myelinated vasomotor nerves and pain fibers, sparing conduction over somatic motor pathways entirely. In short, the method can rather closely approximate the end result expected from surgery as advocated by Smithwick, Grimson, and others for patients with hypertension.

This patient was tilted from the horizontal to a 70° head-up position on a tilting ballistocardiograph prior to receiving differential anesthesia. Some reduction in blood pressure occurred, but at the end of ten minutes of observation in the erect position, circulatory adequacy was still evident. A sensory level (to pin prick) of D-7 was then obtained with dilute procaine and the tilt repeated with the results noted in Fig. 9. The tilt caused lowered blood pressure, probably dependent on vasodilatation, and the absence of pulse acceleration noted in the previous tilt. As the erect position was maintained, the arterial pulse became less and less sustained and cerebral anemia with syncope and twitching occurred; three minutes after the tilt there was no visible heart beat on the tracing. Immediate return to the horizontal fortunately restored circulatory adequacy. The significance of this sequence of events will not be discussed in this paper, although some of its implications are of great interest. The value of continuous arterial pulse tracings under such circumstances is evident.

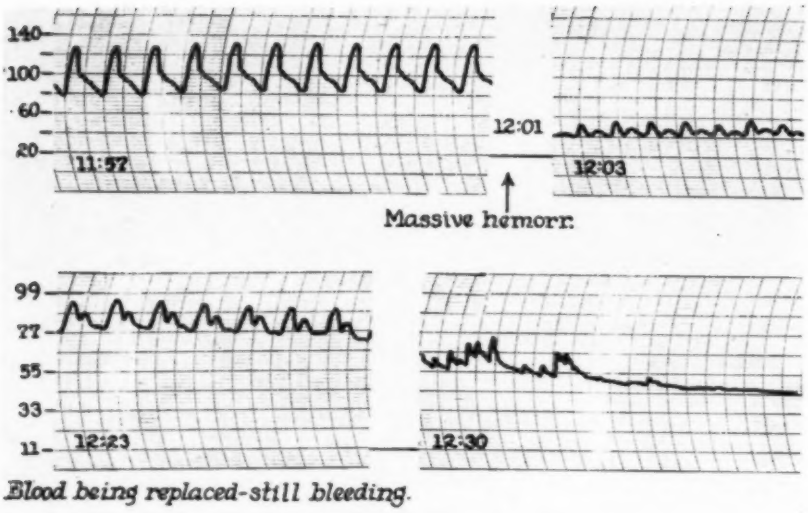


Fig. 8.—Brachial artery tracings from a 55-year-old man undergoing operation for bronchogenic carcinoma. Anesthesia induced at 9:55 with cyclopropane, ether, and oxygen. He was bronchoscoped at 10:05. Controlled respiration begun at 10:45. 11:10: Surgical dissection was begun around the heart. 11:21: Right pulmonary artery was ligated. 11:57: Pericardium was opened. 12:01: A massive hemorrhage occurred from the lung hilus. 12:13: Bleeding still continuing and during a period of six to eight minutes 500 c.c. of blood had been replaced. By 12:23 a total of 3,000 c.c. of blood had been given by syringe. The hemorrhage continued and at 12:30 the heart stopped and the pressure began dropping to 23 mm. of mercury.

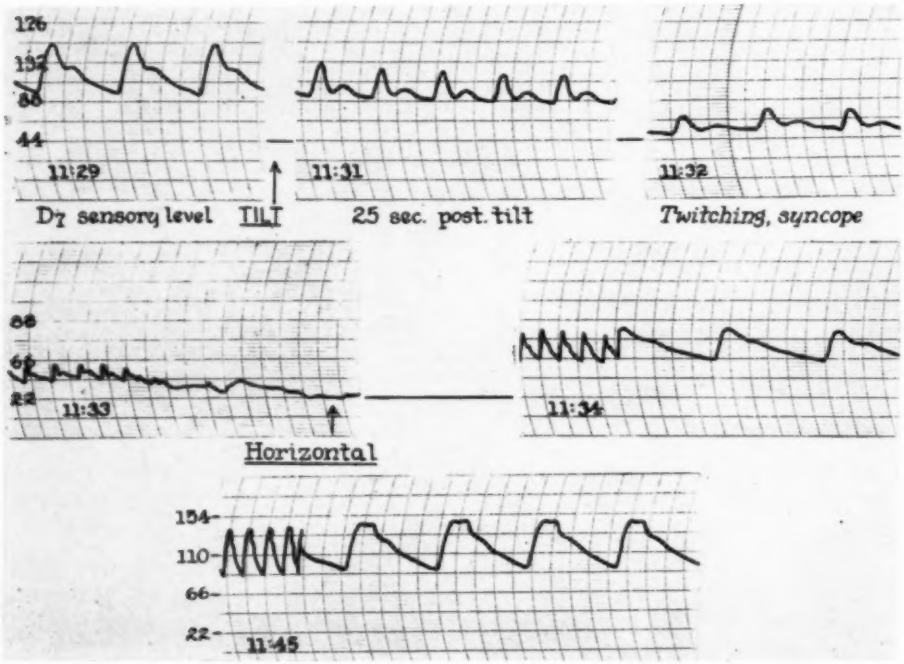


Fig. 9.—Brachial artery pressures from a 42-year-old man under conditions described in text. 11:29 shows the pretilt tracings with abolition of pin prick sensation at D-7. The subject was tilted to the 70° head-up position and the 11:31 record was obtained twenty-five seconds later. The subject became dizzy and at 11:32 twitching with syncope appeared. The pressure continued to fall and at 11:33 distinct beats were not visible in the arterial tracing. The subject was returned immediately to the horizontal position with a return of pulsation and pressure as shown at 11:34. There was abolition of sensation to D-7 from 11:34 through 11:45.

## DISCUSSION

With the method of recording described in this paper, one can transcribe detailed notes directly under the arterial pressure tracings as the paper unrolls from the ink-writer. The elimination of the time lost in developing photographic records makes it possible to correlate cause and effect relationships more accurately and to avoid delay in the application of therapeutic measures if the apparatus is being used under clinical conditions. The method has the further advantage that records can be obtained at a distance of twenty feet from the patient with no other connection to the recording unit than three small flexible conductors. Such recording has been continued for over ten hours and then stopped voluntarily. The method imposes no discomfort on the subject. The equipment can be transferred readily from room to room and from patient to patient. The entire procedure can be maintained under sterile conditions. Records can be taken in the erect, supine, and lateral positions, all awkward positions for recording with the hypodermic manometer. The apparatus can be used under clinical conditions with no disruption of routine. There is relatively little limitation of an investigation imposed by motion of the subject since the catheter can be better maintained in position than a rigid needle. Finally, the Riva-Rocci method of measuring systolic and diastolic pressures is inaccurate under certain conditions.[9,10] A knowledge of the pressures developed with each heart beat, therefore, may often be of great value.

The proposition that pulse pressure patterns indicate changes in the hemodynamics is not new, and for years Wiggers and others have stressed the utility of such curves.[5,10] It is well known that changes in peripheral resistance will produce a different type of alteration in the arterial pulse from the alteration due to changes in stroke volume. Inability to assess the influence on pressure pulse curves of variables such as the elasticity of the blood vessels and the viscosity of the blood have made some workers hesitant in their use. If each record is used as its own control, however, these variables are less significant since they are usually constant enough to be neglected in the interpretation of such gross changes as have been shown in this paper.

## SUMMARY

1. A method for recording arterial pressure pulse waves in man is presented which has certain practical advantages over techniques in current use.

2. Cases are presented to demonstrate the utility of such an apparatus.

3. The application of this method to experimental and clinical procedures provides the observer with an opportunity of investigating large numbers of subjects under a wide range of conditions.[12,13]

The authors wish to thank Dr. H. C. Bazett for advice in the preparation of this paper and Dr. P. R. Dumke, Dr. K. F. Eather, and Dr. L. Wiley for aid in collection of the clinical data.

## ADDENDUM

Since the earlier work reported in this paper was completed, the Moore School of Electrical Engineering has developed an improved amplifier system for use with this procedure. This amplifier has been used in recent work with distinct advantage through improvements in stability and linearity over a wider range and through the greater convenience which it affords. A description of this design appears in the paper which follows. (Tompkins, Howard E.: A New Capacitance-Blood-Pressure-Manometer Amplifier).

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# A NEW CAPACITANCE-BLOOD-PRESSURE-MANOMETER AMPLIFIER

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PHILADELPHIA, PA.

IN THIS paper a new amplifier circuit for use with the Lilly capacitive-type manometer[1] for the measurement of intra-arterial blood pressure is described, and performance data taken with the pilot model are given. The physiological uses of this type of equipment have been described in the preceding paper.[2]

This amplifier, used with a Lilly manometer, will measure from 0 to 370 mm. Hg in five ranges, each range normally starting from 0 but with simple provision for extending each range down to 15 mm. Hg below atmospheric pressure. At maximum sensitivity, 27 mm. Hg gives full scale deflection. The linearity on each range is $\pm 3$ per cent, as shown in Figs. 1 and 2.

The stability of the electrical system is good, as is partially shown in Fig. 3, and the stability of the over-all system tends to be limited by the manometer head rather than the amplifier. Stability with respect to manipulation of the connecting cable between the patient and the amplifier is excellent, being less than the effect of 1 mm. Hg pressure. The equipment may readily be used at distances of the order of twenty feet from the patient, or at longer distances with a special cable.

The necessary bandwidth for accurate representation of blood pulse wave forms extends from 0 (direct current) to at least 70 cycles per second.

The capacitance of the Lilly manometer will change 6 micromicrofarads from an initial 125 micromicrofarads under an applied hydrostatic pressure of 300 mm. of mercury. This change requires an extremely small volume of fluid; hence the inertia of the liquid system is small, and the capacitance is able to follow pulse wave variations of from 0 to 70 cycles per second or well over 100 cycles per second, depending on the catheter used. A study of the precise bandwidth of such fluid systems is in progress.

The output of the amplifying system must be presented in a clear, permanent form, so that the record of the pulse and average pressure may be studied after the actual measurement (or operation) is concluded. For clinical use, however, the record must also be immediately visible during the measurement. An ink-writing galvanometer is the most convenient instrument on which to present the information.

Alternatively, a conventional mirror galvanometer using photographic recording may be used. In this case the pulse wave form can be observed on a good medium-persistence cathode-ray oscillograph, and the average blood pressure may be observed instantaneously with a direct current milliammeter. This set-up is considerably more clumsy than the ink-writer.

The circuit described herein, which is being produced commercially,* in slightly modified form, is designed specifically to drive an ink-writer,† but will

From the Moore School of Electrical Engineering, University of Pennsylvania.
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*By Technitrol Engineering Co., 3212 Market Street, Philadelphia 4, Pa.

†Such as Model BL-201 or BL-202 Oscillographs manufactured by the Brush Development Co., 3405 Perkins Ave., Cleveland 14, Ohio.

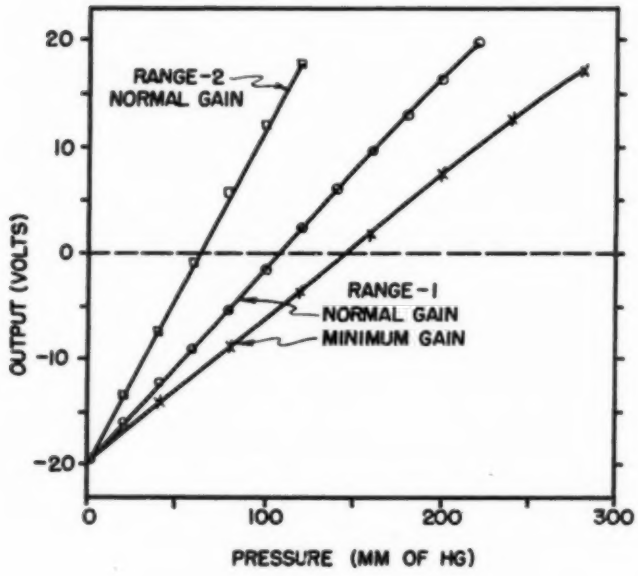


Fig. 1.—Deflection of 1,500 ohm ink-writing galvanometer versus pressure at Lilly manometer head for Ranges 1 and 2 at normal gain and Range 1 at minimum gain. One volt corresponds to a galvanometer deflection of 1.05 millimeter.

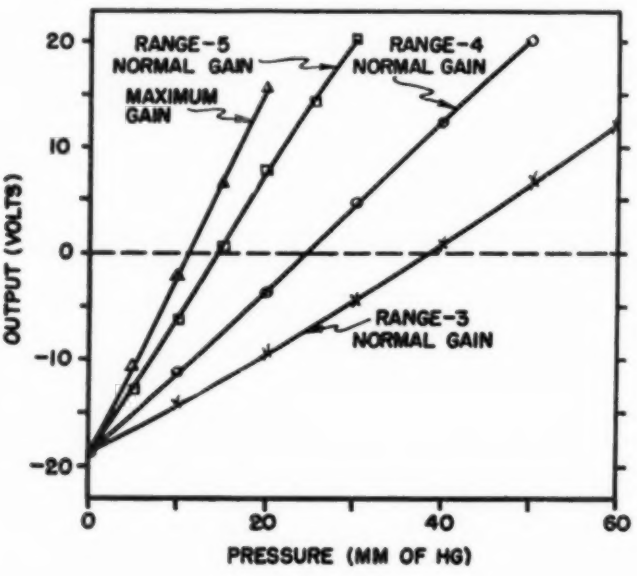


Fig. 2.—Deflection of 1,500 ohm ink-writing galvanometer versus pressure at Lilly manometer head for Ranges 3, 4, and 5 at normal gain and Range 5 at maximum gain. One volt corresponds to a galvanometer deflection of 1.05 millimeter.

also drive any other common type of indicating instrument. The bandwidth of the electrical system using the ink-writer is shown in Fig. 4.

This particular circuit is not the only one that has been used with capacitance blood pressure manometers. Other systems have been described and built by Skouby and others[3,4] in Denmark.

The circuit is applicable to any measurement problem in which the desired information can be observed as a capacitance variation. Output versus capacitance change is shown in Fig. 5. Other medical and nonmedical uses for the equipment should, therefore, develop.

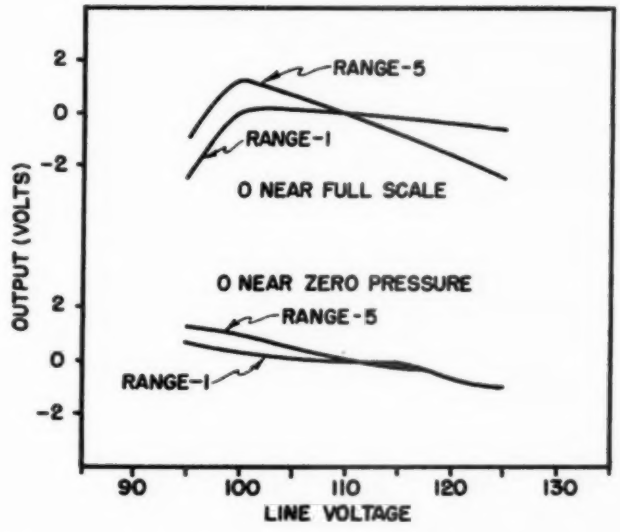


Fig. 3.—Variation of zero reading and a reading near full scale on Ranges 1 and 5 versus 60 cycle line voltage applied to unit.

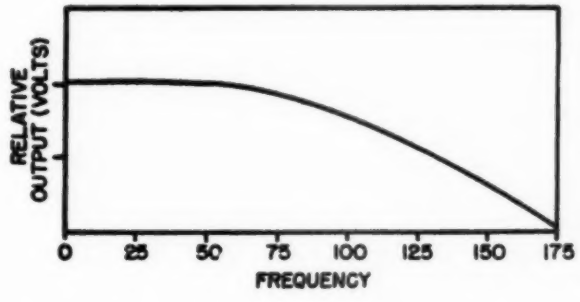


Fig. 4.—Frequency response of electrical system from radio frequency bridge through ink-writing galvanometer. The falling high frequency response of the galvanometer is compensated for by the amplifier.

A block diagram of the system is shown in Fig. 6 and a detailed schematic representation in Fig. 7. The capacitive manometer head is part of one arm of an alternating current bridge which, although adjusted for exact resistive balance, is slightly unbalanced reactively. When the blood pressure varies, the

capacitance of the manometer head varies, and the reactive unbalance of the bridge is increased, thus increasing the transmission of the bridge.

A radio frequency (2.2 megacycles) constant amplitude oscillator drives the input of the bridge. The output voltage of the bridge is thus proportional to the unbalance caused by the blood pressure. This voltage, still a radio frequency alternating wave, is then amplified by a two-stage tuned amplifier, shown on the block diagram as the R. F. Amplifier. Any convenient frequency may be used. The choice of 2.2 megacycles was dictated by the capacitance of the manometer head and the available space for a coil to resonate it.

The amplified radio frequency signal is detected by a vacuum diode (part of the 6AT6 tube) and the resulting pulsating direct voltage is a replica of the instantaneous blood pressure at the manometer head. This voltage is amplified in the two-stage direct coupled amplifier to a power level sufficient to drive the recording galvanometer.

The output circuit, in the cathode of the 6AQ5 tube, is designed to drive a 1,500 ohm ink-writer, whose rest position is at mid-scale. Accordingly, the output voltage can vary from 23 volts negative to 23 volts positive about ground (or chassis), when a 1,500 ohm load is connected at Output 1. Alternatively a low impedance galvanometer may be used at Output 2 (see Fig. 2). By appropriate adjustment of the zero-set control, the amplifier can be used with an indicating instrument, the rest position of which is at zero pressure, that is, at one end of the instrument scale.

The output circuit saturates immediately beyond the stated output power and the output voltage will not keep rising. This feature protects the indicating instrument from damage. It is essential that some such protection be provided in a circuit of this type, for without it the indicating instrument would be overloaded severely if the manometer head were disconnected or if the zero set knob were twisted inadvertently.

The range control switch in the radio frequency amplifier provides five different pressure sensitivities, which at normal gain control setting require 35, 60, 90, 160, and 270 mm. Hg pressure, respectively, for full scale (5.0 cm.) deflection (a total voltage swing of about 46 volts). The gain control in the detector circuit will increase or decrease the sensitivity of each range about 1.4 to 1; thus, it provides any desired intermediate sensitivity between ranges and extends Range 1 up to 370 mm. Hg full scale and Range 5 down to 27 mm. Hg, full scale.

By adjustment of the zero set control the bottom of the scale on each range can be set anywhere from −15 mm. Hg (that is, below atmospheric pressure) to approximately one-half full pressure for that range. This allows expansion of a pulse wave if desired, and extends the range of the instrument to slightly higher pressures.

In all, only three controls are used in operating the instrument: the range, gain, and zero set controls. Bridge alignment, which should be checked every few weeks, requires the adjustment of four controls which are available at the side of and inside the case. A simple check on bridge alignment is possible from the front panel as the zero will shift from range to range if the bridge is not aligned correctly for the particular manometer head being used.

The stable performance of this circuit is due largely to the following factors:

1. A small coil is mounted in the manometer head, and is connected in a series between the head capacitance and the coaxial transmission line leading back to the main chassis. The inductance of this coil resonates with the head capacitance at the radio frequency being used (2.2 megacycles). Thus, the coaxial transmission line connecting the patient with the equipment is at low impedance (about 20 ohms) and variations in its capacitance have very little effect on the output.

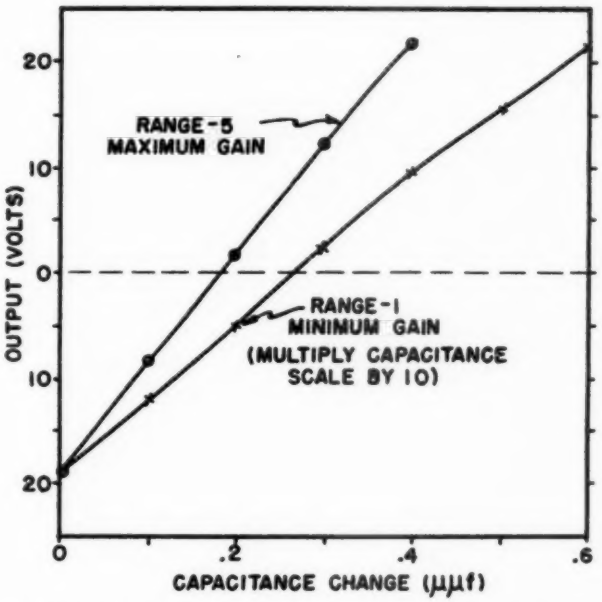


Fig. 5.—Deflection of 1,500 ohm ink-writing galvanometer versus capacitance change at input on Ranges 1 and 5 at extreme gains. Note different scales.

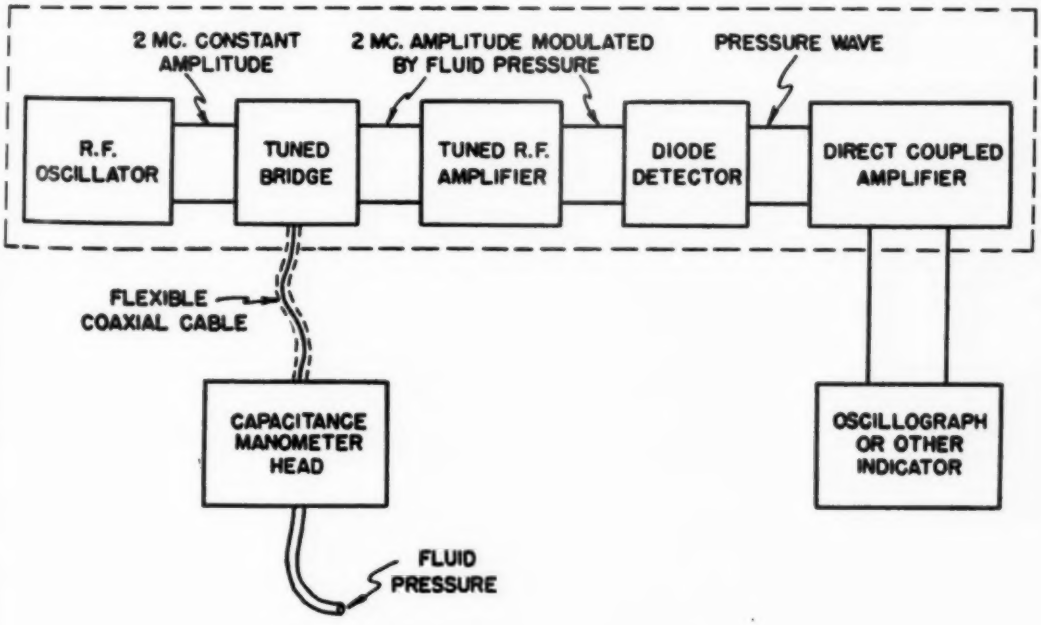


Fig. 6.—Block diagram of manometer amplifier system.

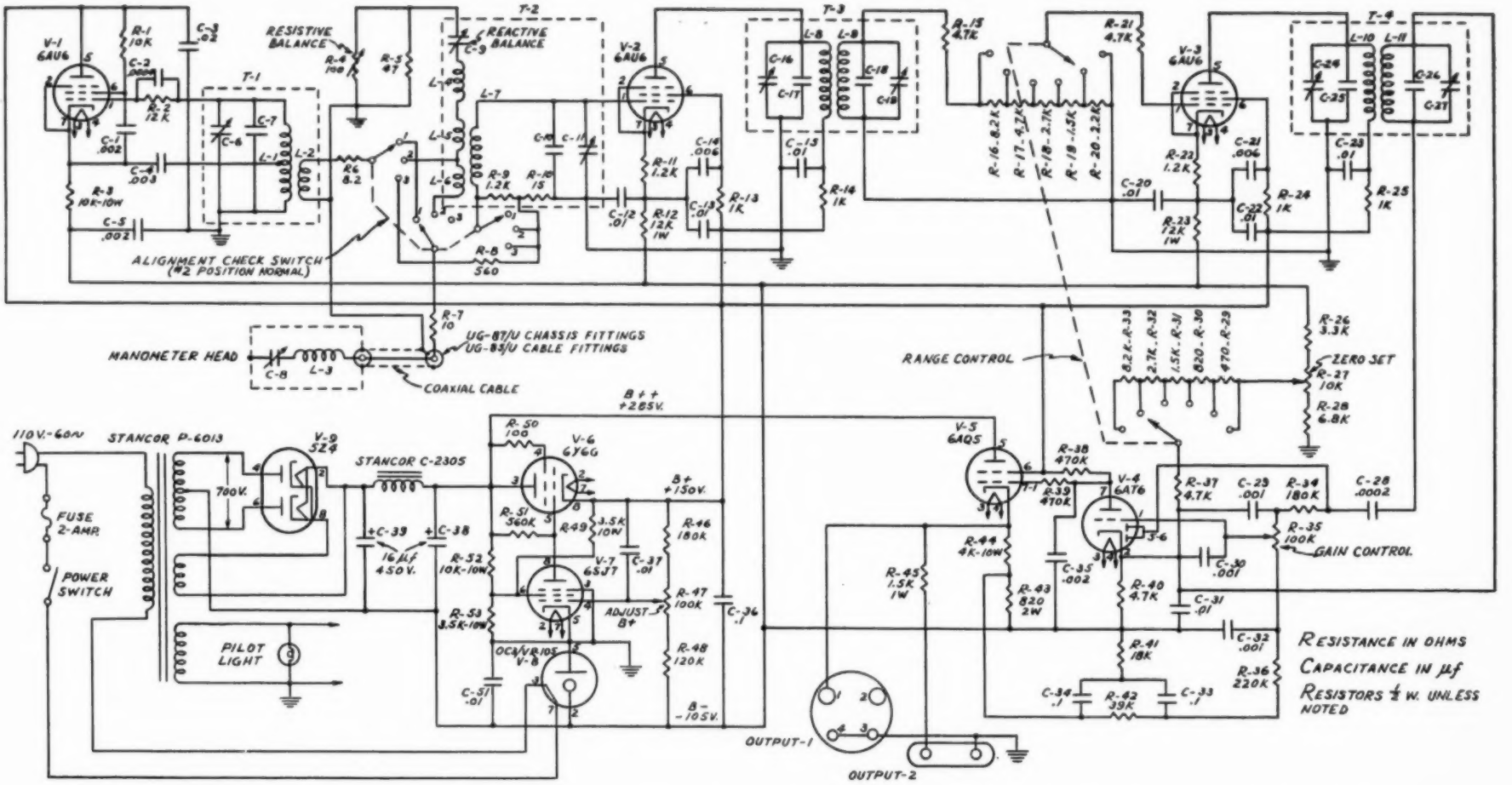


**Fig. 7.—Schematic diagram of capacitance-blood-pressure-manometer amplifier.** *T-1* is a 2.2 megacycle oscillator tank circuit with an 8 ohm output winding. Oscillator output is 0.7 volts at the output winding. *T-2* is the radio frequency bridge transformer. Windings *L-5* and *L-6* are four turns each, balanced 1/16 inch from tuned secondary winding *L-9*. Coil *L-4* and its trimming capacitor *C-9* are tuned to 2.2 megacycles and form the major part of one arm of the bridge. *T-3* and *T-4* are conventional critically coupled interstage transformers. The manometer head (*L-3* and *C-8*) is tuned to 2.2 megacycles. Alignment check switch is normally in Position 2 during use. Position 1 is used in aligning the oscillator to the frequency of the head. Position 3 is used in checking the circuit in the absence of a manometer head. For production, the detail of this circuit has been modified by the Technitrol Engineering Co.

2. The use of a radio frequency amplifier system obviates the need for a high-gain direct-coupled amplifier, which would inevitably introduce a great deal of instability. The only direct-coupled amplifier used in this unit is for power amplification at the output, and this two-stage amplifier has a net voltage gain of less than 6. The rest of the available direct-coupled amplifier gain is used to provide inverse feedback for increased stability.

3. Inverse feedback of the signal is used in all the amplifier circuits so that their performance will be relatively independent of tube age and operating conditions.

4. Direct current degeneration is used in both oscillator and radio frequency amplifier circuits to provide stable tube operating points which are relatively independent of heater voltage and tube age.

5. An electronically regulated power supply is used which provides relative freedom from the effects of varying power line voltage over a range from 95 to 130 volts (Fig. 3).

Of course, stability requires, in addition, that all components be operated well within their ratings, and that good quality components be used. For example, only air padders should be used in the tuned circuits of the amplifier.

ACKNOWLEDGMENT

The design of this circuit is based in large part on an earlier version by Mr. Theodore H. Bonn. The author's thanks are due to Dr. H. C. Bazett of the Physiology Department of the University of Pennsylvania for his support and encouragement, and to Mr. L. H. Peterson of the same department for his able presentation of the medical man's point of view toward this device.

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# ELECTROCARDIOGRAPHIC CHANGES FOLLOWING ELECTRO-SHOCK THERAPY IN CURARIZED PATIENTS

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THE therapeutic benefit of electrically induced convulsions in certain neuropsychiatric disorders has in recent years become firmly established. Many of the candidates for this form of treatment are in the middle and older age groups, and the problem is frequently complicated by coexisting cardiovascular disease. The decision regarding what clinical and electrocardiographic abnormalities contraindicate electroshock therapy in such patients is difficult, since there is inadequate knowledge regarding methods of prevention of alarming reactions and mechanisms of fatal outcome. Acute myocardial infarction and aneurysms are usually considered absolute contraindications to electroshock therapy. Yet we are aware of one acutely suicidal patient of Dr. Titus Harris[1] who had an acute myocardial infarction and survived electroshock therapy. He has also treated without difficulty a patient with a severe, agitated depression who had a large thoracic aneurysm. Although it is generally agreed that cardiovascular disease adds to the risk of therapy, the indications for treatment may be so urgent that they outweigh this increased risk.

Reported fatalities are relatively rare, and were reviewed by Ebaugh and associates[2] and more recently by Will, Rehfeldt, and Neumann.[3] The latter authors collected records of thirty-three deaths from electroshock in the American and English literature, fifteen of which occurred immediately or shortly after the application of the electrical stimulus. The causes of the sudden deaths remain obscure, since clinical descriptions of the respiratory and cardiac systems are not conclusive, and an electrocardiogram has never been taken during exitus in such situations. The pathology found at post-mortem examinations is usually not adequate to explain the cause of death. Kalinowsky and Hoch[4] believe that most fatalities are cardiovascular in origin, although respiratory complications are more common.

Curarization before treatment is frequently a routine procedure, its purpose being to decrease the severity of the convulsions and to lessen the increased

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From the Psychiatric and the Cardiovascular Services of the University of Texas Medical Branch, Galveston, Texas.

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cardiac burden imposed by the violent muscular exercise. Several investigators believe that the pretreatment use of this drug leads to additional dangers, and we have had knowledge of one death from curarization alone. Lowinger and Huddleston[5] suggested that curare played an important role in the causation of marked variability in blood pressure, pulse, and respiration noted in curare-preceded electrical convulsions. Woolley[6] was able to abolish these with adrenalin or Prostigmine. Jones and Pleasants[7] have advised the cautious use of curare in patients with severe cardiac disease, believing that the period of apnea after the convulsion is thereby prolonged to aggregate myocardial ischemia from sclerotic vessels. In a report of a series of twenty-one cardiac and noncardiac patients studied here, no electrocardiographic changes were found after curarization,[8] but this does not absolve curare as a contributing factor. Intravenous Prostigmine is usually given for respiratory difficulty following the convulsion, in an attempt to counteract the aggravation of anoxia caused by curare-induced muscular weakness.

In 1941, Bellet, Kershbaum, and Furst[9] reported an electrocardiographic study during and after sixty-five electrically induced major seizures and thirty-five minor seizures in fifty patients with normal cardiovascular systems. Changes were noted as being less frequent and less severe than those that had been observed in Metrazol therapy and in insulin shock therapy. Following the convulsion there was frequently a slowing of rate which was considered to be vagal in origin and which, in three cases, was abolished by atropine. In one patient given curare before the electrical stimulus, idioventricular rhythm followed the convulsion, but it was absent after a later treatment in which curare was omitted. Kline and Fetterman[10] in 1942 summarized studies of Lead II and in some cases a single apical lead immediately after the electroshock convulsion in forty-two psychotic patients. Cardiac arrhythmias were not conspicuous, and an elevated T wave was noted in all but eight cases. Five patients with cardiovascular disease showed no unusual changes. In 1943, Nyman and Silfverskiöld[11] took electrocardiograms immediately after electroshock convulsions in thirteen patients. They found a rise in $P_2$ and $T_2$ and a fall in $R_1$. On the basis of similarity of these changes to changes after the Valsalva maneuver, these investigators considered the mechanism in the two conditions to be the same. Altschule, Sulzbach, and Tillotson[12] recorded electrocardiograms before and after thirty seizures in ten patients, noting frequent arrhythmias of apparent vagal origin. The uniform increase in height of P waves was attributed to dilatation of the atria after the convulsion, and alterations in the ventricular complexes were not considered significant. Evans[13] observed transient changes apparently indicating improvement in the electrocardiograms of five patients with heart disease following electroshock. These changes consisted mainly in reversal of negativity or increase in height of T waves.

The present study of the effects of electroshock upon the electrocardiogram in curarized patients was stimulated by observation of several alarming post-treatment reactions and two deaths which immediately followed treatment and apparently were due to cardiac arrest. These two fatalities have been reported in detail[14] and occurred immediately after the initial treatment in a 16-year-old

Mexican girl and after the seventh convulsion in a 70-year-old white woman. Unfortunately, no tracings were taken during exitus, but the pretreatment electrocardiograms are shown in Fig. 1.

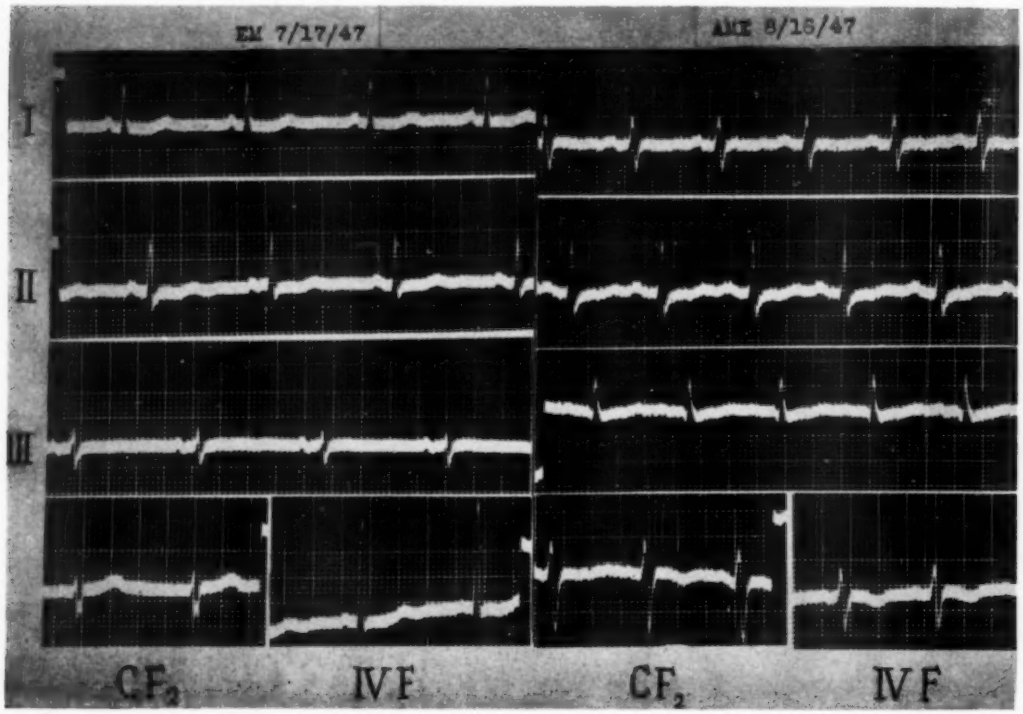


Fig. 1.—Electrocardiograms before treatment of two patients with fatal reactions after electroshock. E. M., a 70-year-old white woman, expired immediately after the seventh treatment. The Q-T interval is 0.40 second, the upper normal for the rate of 70 per minute. A. M. E., a 16-year-old Mexican girl, expired after the first electroshock convulsion, from apparent cardiac arrest. The P-R interval is 0.22 second, and the rate is 94 per minute. The T wave is flat in Lead 1, low in Leads II and III, and negative in Lead $CF_2$ and IVF.

## CLINICAL MATERIAL STUDIED AND METHODS USED

The cardiovascular status of each patient was evaluated by means of a painstaking history, complete physical examination, and electrocardiogram with routine chest leads ($CF_2$ and $CF_4$). Curarization was than accomplished before each treatment with d-tubocurarine chloride given intravenously at a rate of 1.0 c.c. per minute. The dosage was 0.05 c.c. (1 unit) per kilogram of body weight less a safety factor of 0.5 to 1.0 c.c., depending on the degree of relaxation achieved. A base-line tracing consisting of all three limb leads was taken with a Sanborn Viso-Cardiette, a rugged, direct-writing electrocardiograph, after completion of curarization and immediately preceding the application of the electrical stimulus with the Electra conventional stimulator. The limb leads were left in place and as much of a continuous tracing in Lead II as possible was taken during the tonic and clonic phases of the convulsion. Immediately after the

convulsive movements ceased, beginning with Lead II, a continuous tracing with all three limb leads was recorded as long as rapid changes were taking place. Then intermittent tracings were taken at brief intervals until the electrocardiogram had returned to its pretreatment form, usually five to ten minutes after the convulsion. In a few of the patients with postconvulsive respiratory difficulty, 1.0 c.c. of 1:2,000 Prostigmine methylsulfate was given intravenously after one to two minutes of tracings had been obtained.

Using this procedure, a series of 304 tracings was obtained before, during, and after major convulsions in 126 consecutive curarized patients. In twenty-three instances tracings were also taken during preliminary petit mal reactions in these patients. No deaths were encountered. A summary of the age and sex of the patients, with the number of electrocardiograms taken, is given in Table I. The psychiatric diagnoses were: psychotic depression, 70; manic, 5; schizophrenia, 32; others, 19.

TABLE I. AGE AND SEX DISTRIBUTION OF CLINICAL MATERIAL

| | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | TOTAL | |
|---|---|---|---|---|---|---|---|---|---|
| Male patients | 1 | 3 | 7 | 14 | 8 | 4 | 2 | 39 | |
| Electrocardiograms | 2 | 11 | 12 | 28 | 25 | 7 | 4 | | 89 |
| Female patients | 2 | 10 | 21 | 21 | 23 | 8 | 2 | 87 | |
| Electrocardiograms | 5 | 29 | 42 | 51 | 62 | 22 | 4 | | 215 |
| Number patients | | | | | | | | 126 | |
| Number electrocardiograms | | | | | | | | | 304 |

## DETAILS OF THE ELECTROCARDIOGRAPHIC FINDINGS

Satisfactory electrocardiograms were recorded during the tonic phase in fifty-one major convulsions in thirty-six patients, and in three instances the entire tonic and clonic portions were obtained. Excerpts from one of these records are shown in Fig. 2. Immediately following the stimulus, all such tracings showed a gradually increasing sinus tachycardia, which reached a rate at the end of the tonic phase averaging 35 per minute over the beginning value. Single premature ventricular contractions were observed during the tonic portion of the convulsion in three cases, and in one there was transient atrial fibrillation. Twenty-three petit mal episodes were also recorded, four patients having two such successive reactions and two having three. In each instance increasingly stronger electrical stimuli were applied until a major convulsion was finally produced. Ten of the petit mal reactions were accompanied by decreases in sinus rate varying from 5 to 50 per minute, seven by no rate change, and six by increases of 5 to 30 beats per minute.

An analysis of the patients showing clinical or electrocardiographic evidence of heart disease is presented in Table II. It seemed desirable to compare the changes of rhythm noted in this series of tracings with the changes observed in patients with apparently normal hearts, since such comparisons had not been

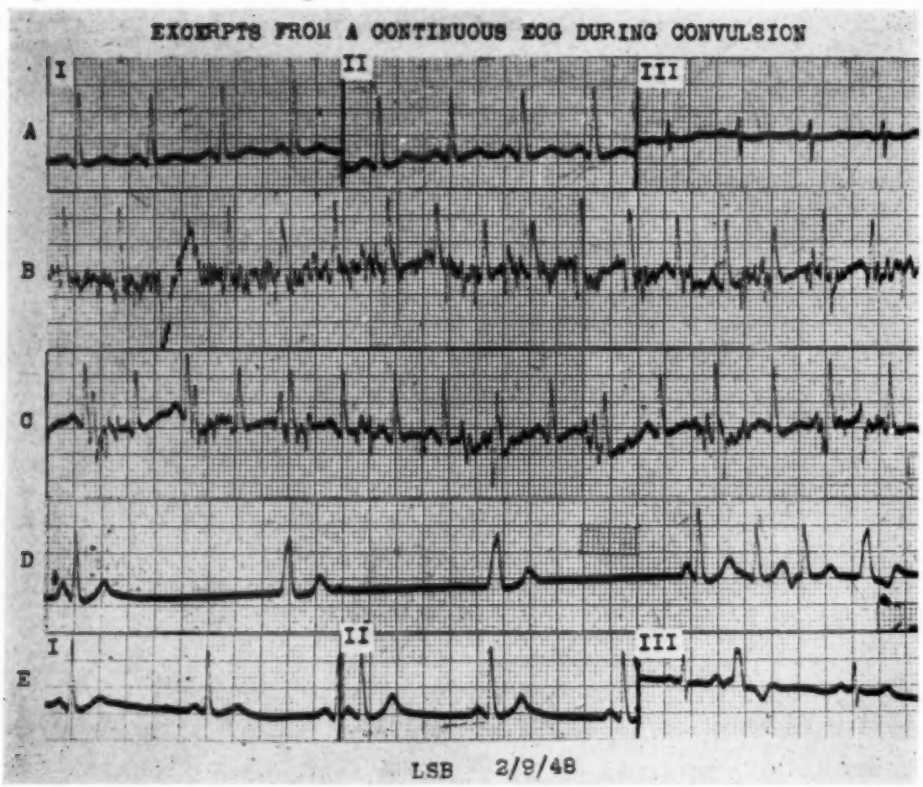


Fig. 2.—Excerpts from a continuous tracing made during and after major convulsion in L. S. B., a 55-year-old white man with no evidence of heart disease. *A*, Limb Leads I, II, and III before the electrical stimulus. *B*, Lead II during the tonic phase, showing premature ventricular contraction. *C*, Clonic phase, with rapid sinus tachycardia. *D*, Lead II immediately after the end of the convulsion; temporary suppression of sinus pacemaker with impulses initiated in A-V bundle, followed by short run of ectopic atrial impulses. *E*, Limb Leads I, II, and III one minute later with T-wave elevation in each. Tracing taken five minutes later showed a form similar to that shown in *A*.

TABLE II. ANALYSIS OF PATIENTS WITH HEART DISEASE

| | NO. PATIENTS | NO. ECG |
|---|---|---|
| Definite ECG evidence of myocardial damage | 7 | 20 |
| ECG suggestive of damage with positive clinical signs of heart disease | 15 | 37 |
| ECG negative, with clinical evidence of heart disease | 4 | 13 |
| Total | 26 | 70 |

made previously. In the pretreatment electrocardiograms, there were occasional premature ventricular contractions in two patients with heart disease and in one patient with a normal heart. Nodal ectopic beats occurred in the base-line tracing of one patient with heart disease. Table III shows a summary of all the disorders of rhythm, these generally beginning immediately after the last con-

vulsive twitch and being completed within five minutes. Illustrative electrocardiograms showing some of the more striking changes are included in Figs. 3, 4, and 5.

TABLE III. ARRHYTHMIAS FOLLOWING 304 MAJOR CONVULSIONS AFTER ELECTROSHOCK

| | CV DISEASE 70 ECG | | NO CV DISEASE 234 ECG | | TOTAL 304 ECG | |
|---|---|---|---|---|---|---|
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| Sinus arrhythmia | 8 | 11.4 | 27 | 11.5 | 35 | 11.5 |
| Ectopic beats, atrial | 33 | 47.1 | 56 | 19.7 | 89 | 26.0 |
| Ectopic beats, ventricular | 28 | 40.0 | 29 | 12.4 | 57 | 18.7 |
| Ectopic beats, nodal | 5 | 7.1 | 13 | 5.5 | 18 | 5.9 |
| Wandering pacemaker | 23 | 32.9 | 23 | 9.8 | 46 | 15.1 |
| Nodal rhythm | 16 | 22.9 | 28 | 12.0 | 44 | 14.5 |
| Transient S-A standstill | 0 | 0 | 6 | 2.6 | 6 | 2.0 |
| Blocked S-A impulses | 8 | 11.4 | 4 | 1.7 | 12 | 3.9 |
| Prolonged P-R interval | 7 | 10.0 | 7 | 3.0 | 14 | 4.6 |
| Wenckebach phenomenon | 0 | 0 | 2 | .9 | 2 | .7 |
| 2:1 A-V block | 0 | 0 | 2 | .9 | 2 | .7 |
| Parox. atrial tachycardia | 1 | 1.4 | 1 | .4 | 2 | .7 |
| Atrial fibrillation | 0 | 0 | 1 | .4 | 1 | .3 |
| Idioventricular rhythm | 0 | 0 | 2 | .9 | 2 | .7 |
| Ventricular tachycardia | 0 | 0 | 1 | .4 | 1 | .3 |
| Bigeminy (vent. pre. con.) | 3 | 4.3 | 0 | 0 | 3 | 1.0 |
| Trigeminy (vent. pre. con.) | 0 | 0 | 1 | .4 | 1 | .3 |
| *Number of Above Arrhythmias in Each ECG* | | | | | | |
| No rhythm disturbance | 13 | 18.6 | 108 | 46.1 | 121 | 40.0 |
| One rhythm disturbance | 21 | 30.0 | 73 | 31.2 | 94 | 30.9 |
| Two disturbances | 19 | 27.1 | 33 | 14.1 | 52 | 17.1 |
| Three or over | 17 | 24.3 | 20 | 8.5 | 30 | 9.9 |
| *Tachycardia and Bradycardia* | | | | | | |
| Sinus tachycardia over 135 per minute | 31 | 44.3 | 123 | 52.6 | 154 | 50.7 |
| Sinus bradycardia less than 60 per minute | 1 | 1.4 | 20 | 8.5 | 21 | 6.9 |
| Both sinus tachy. and brady. in same ECG | 0 | 0 | 5 | 2.1 | 5 | 1.6 |

*The T-Wave Changes.*—In Table IV are summarized the changes in the P waves, RS-T segments, and T waves after the convulsive episodes. No significant difference was observed in this regard between patients with heart disease and patients with normal hearts. There were changes of the type usually accepted as evidence of improvement in thirteen electrocardiograms of eleven patients showing suggestive or definite electrocardiographic evidence of myocardial damage before the convulsion. These changes consisted in higher T waves in Leads I and II in five instances and in all limb leads in the other eight tracings.

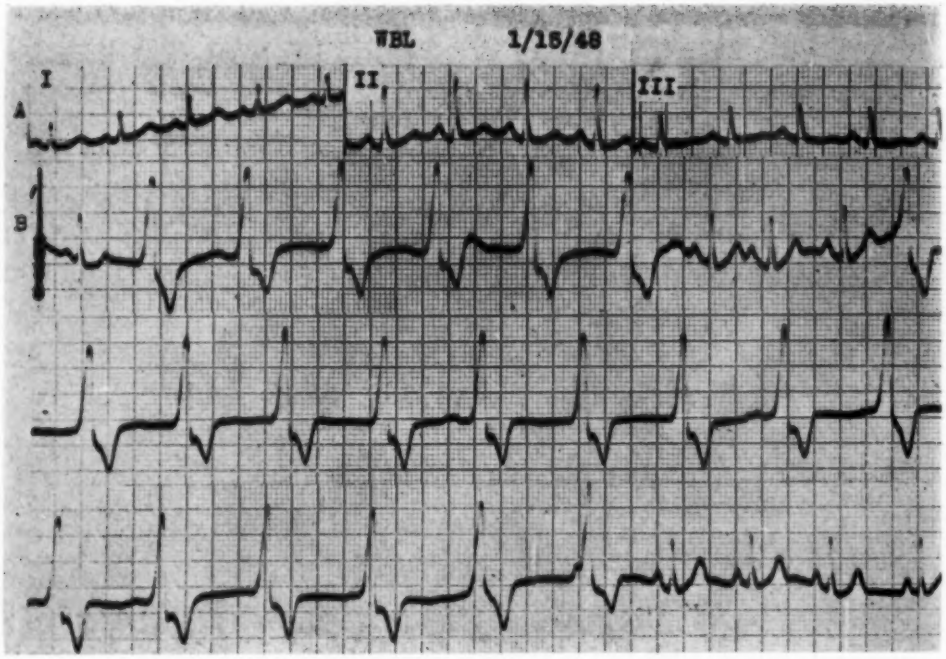


Fig. 3.—*A*, Pretreatment limb leads I, II, and III. *B*, Lead II following convulsion in W. B. L., a 54-year-old white woman without evidence of heart disease. Note the runs of idioventricular rhythm at the rate of 78 per minute, with retrograde P waves. $T_2$ is elevated and RS-$T_2$ is slightly depressed in the portion showing sinus rhythm.

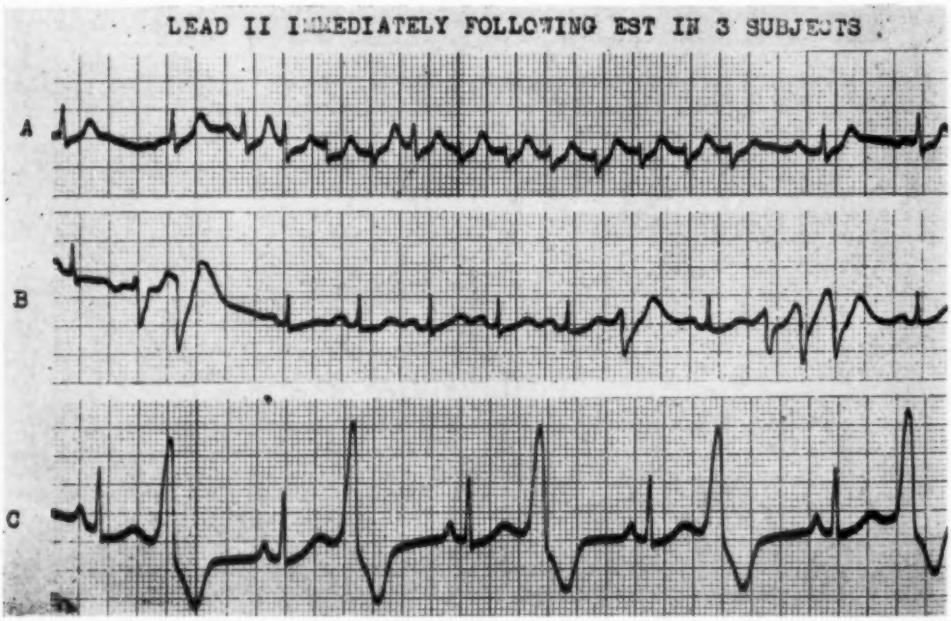


Fig. 4.—Lead II in three subjects immediately following electroshock therapy. *A*, Brief episode of paroxysmal atrial tachycardia in moderately hypertensive 67-year-old white woman with suggestive electrocardiographic signs of myocardial damage. *B*, Ventricular ectopic beats in rapid runs of two and three in a 50-year-old white woman with no evidence of heart disease. Marked respiratory difficulty and cyanosis followed the convulsion, and inhalation of pure oxygen seemed to clear up the premature contractions. *C*, Bigeminy with ventricular premature contractions in a 48-year-old white woman with blood pressure 184/120 and suggestive electrocardiographic evidence of myocardial damage. This was prevented in later convulsions with quinidine sulfate, orally.

The alterations were only temporary, since the T waves had decreased to the original voltage in five minutes. Fig. 6 is presented as an example of such increase in height of T waves in a patient with no heart disease.

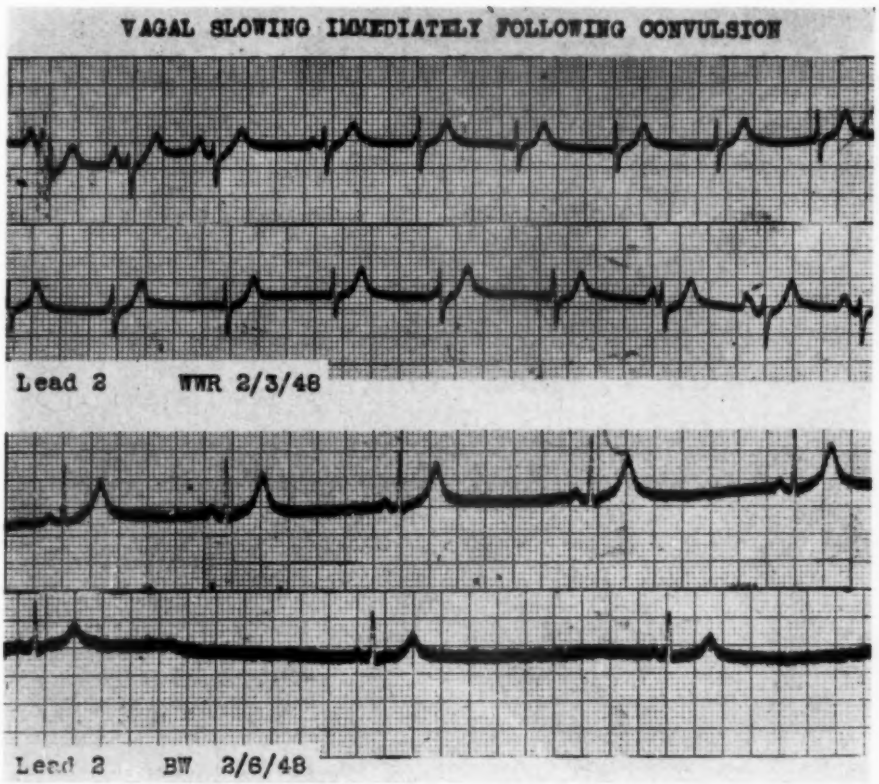


Fig. 5.—W. W. R., a 41-year-old white man with no evidence of heart disease. Tracing shows displacement of pacemaker to A-V node and its return. B. W., a 43-year-old white woman with no heart disease. Convulsion is followed by marked sinus bradycardia, rate 25 per minute.

TABLE IV. CHANGES IN P WAVE, RS-T SEGMENT, AND T WAVE IN 304 ELECTROCARDIOGRAMS AFTER MAJOR CONVULSIONS IN ELECTROSHOCK THERAPY

| | LEAD I | | LEAD II | | LEAD III | |
|---|---|---|---|---|---|---|
| P wave | Higher | 21 | Higher | 154 | Higher | 116 |
| RS-T segment | Depressed | 68 | Depressed | 212 | Depressed<br>Elevated | 106<br>1 |
| T wave | Higher<br>Lower | 158<br>2 | Higher<br>Lower | 192<br>2 | Higher<br>Negative | 156<br>1 |
| No changes in RS-T and T | 127 | | 36 | | 90 | |

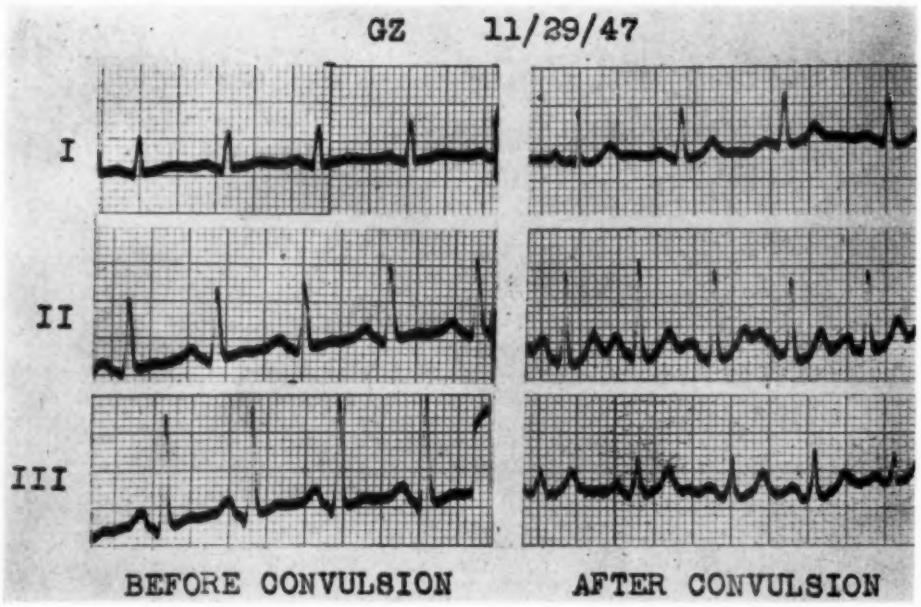


Fig. 6.—Limb leads I, II, and III on G. Z., an 18-year-old white man with no evidence of heart disease. Tracings immediately after electroshock show conspicuous rise in T waves and shift in electrical axis.

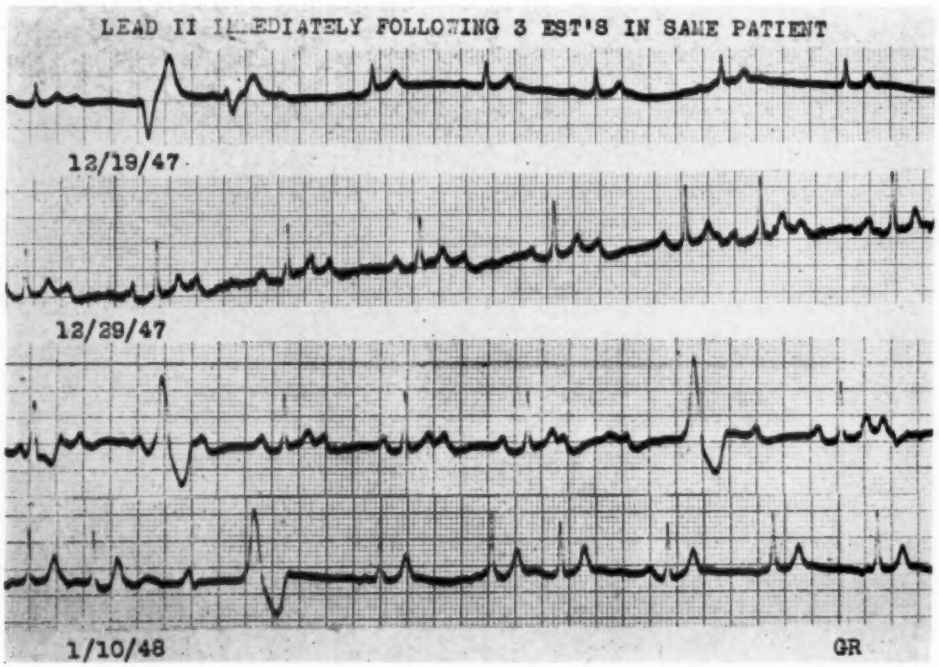


Fig. 7.—Lead II immediately after three different electroshock convulsions on G. R., an 18-year-old white man with no evidence of heart disease. Dec. 12, 1947: Blocked premature atrial impulse followed by two ventricular ectopic beats. Dec. 19, 1947: Periods of 2:1 A-V block. Jan. 10, 1948: Blocked S-A impulses, 2:1 A-V block, and atrial and ventricular ectopic beats. Each convulsion was followed by marked apnea and cyanosis.

*Analysis of Serial Tracings.*—A comparison was made of successive tracings of each of the twenty-seven patients in whom electrocardiograms had been taken during and after four to seven electroshocks. In seventeen of these patients all electroshock treatments produced essentially the same electrocardiographic changes. In five other patients there were minor variations in form and rhythm following different electroshock treatments, and in the five remaining patients there was definite alteration of response. Fig. 7 shows the arrhythmias immediately after three grand mal seizures in a 20-year-old white man which were all apparently due to increase in vagal tone. A series of tracings in one patient showed gradual improvement in the pretreatment curves, each showing more improvement of a temporary nature immediately after the convulsion. In only one case was there electrocardiographic evidence of increasing myocardial damage on successive electroshock treatments. This patient was a 57-year-old white man whose electrocardiograms are shown in Fig. 8. Increasing subendocardial ischemia was held responsible for a progressive depression of the RS-T segments, which was more marked immediately after each convulsion. In a final tracing a week after the last treatment, the RS-T segments had returned to a normal level.

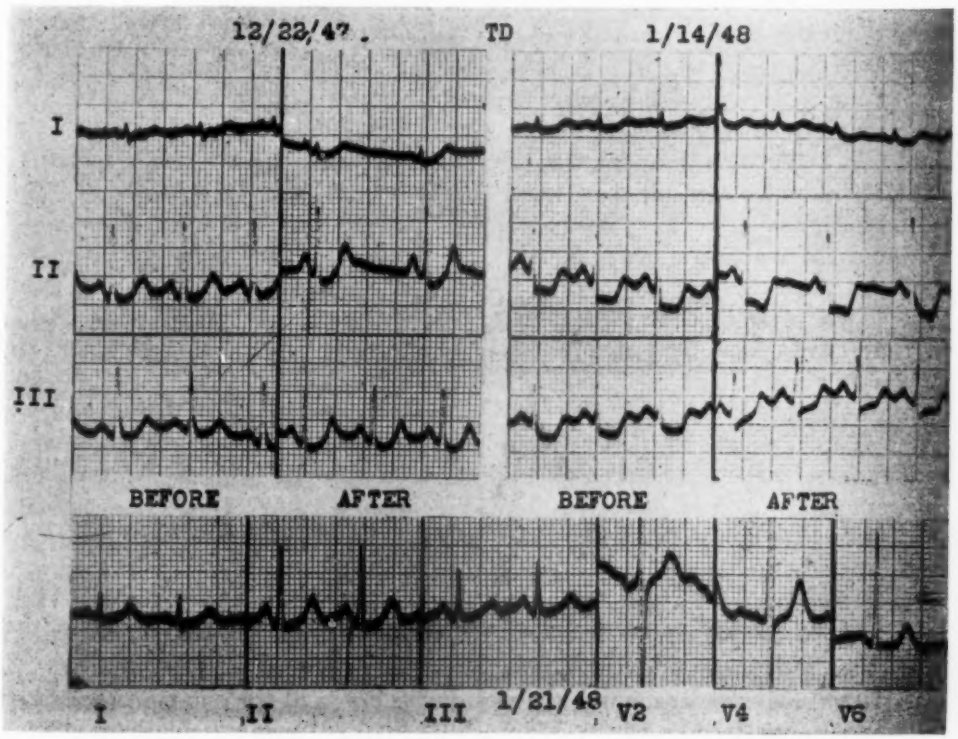


Fig. 8.—Limb leads I, II, and III on a 57-year-old asthenic white man, with original electrocardiogram (Dec. 22, 1947) suggestive of myocardial damage (depression of RS-$T_2$ and RS-$T_3$). Note the increasing depressions of RS-T in Leads II and III, and sag of RS-T in Lead I, temporarily made worse by the convulsive episodes of Jan. 14, 1948. Electrocardiograms taken one week following the last electroshock convulsion, Jan. 21, 1948, shows RS-T segments to have regained their normal level.

*The Q-T Interval.*—A comparison of the Q-T intervals of same cycle lengths in fifty electrocardiograms before and after convulsions revealed a decrease in forty-four instances, no change in five, and an increase in one. The average shortening of the Q-T interval in each case was .038 second. This may well have been a persistence of the effect of the preceding more rapid rate. The QRS complex was often observed to change in height with respiration, particularly in Lead III.

*Pretreatment or Prophylactic Treatment.*—Preliminary investigations of the value of quinidine and atropine as pretreatment medication were then carried out in selected patients showing potentially serious post-treatment reactions. The results in these cases are considered separately from the original series.

In two patients in whom the base-line electrocardiogram showed evidences of myocardial damage, frequent premature ventricular contractions were noted, beginning after one to two minutes of cyanosis which followed the convulsive seizure. These extrasystoles were abolished in one case and markedly diminished in another by quinidine given orally in dosages of 0.2 Gm. four times daily. In another patient with no evidence of heart disease, many premature contractions of ventricular origin were observed immediately after treatment and then were prevented in subsequent treatments with similar quinidine therapy. It was also noted that early administration of 100 per cent oxygen tended to erase ventricular premature contractions.

In the treatment of the arrhythmias of apparent vagal origin, atropine sulfate was given intramuscularly before electroshock, first in doses of grain 1/150 and grain 1/100 with disappointing effects. Later nine patients with posttreatment arrhythmias attributed to vagal effects were treated with atropine, grain 1/50, intramuscularly, thirty minutes before the stimulus. In six of these patients in whom the reaction did not appear severe clinically, this dosage of atropine abolished the electrocardiographic changes in four and greatly decreased them in two. Two patients showed alarming post-treatment reactions, with nodal rhythm of thirty and forty-five beats per minute, respectively, and little improvement was noted after Prostigmine. In these two patients atropine, grain 1/50, before subsequent treatments markedly lessened the duration and degree of cyanosis and apnea, and the electrocardiographic changes were much less severe. One of these patients was then given grain 1/30 atropine before treatment, and this completely abolished the arrhythmia previously present. In the final patient, cardiac slowing due to nodal rhythm was accompanied in several treatments by retching and vomiting during and after the convulsive seizure. Atropine sulfate, grain 1/50, given on several occasions abolished the gastric symptoms in each instance, and the vagal effects disappeared from the electrocardiogram.

The rate immediately before the stimulus after premedication with atropine was 120 to 130 beats per minute, the mouth was dry, and the pupils were slightly dilated. In most cases where grain 1/50 was used intramuscularly, the rate remained constant during and after the convulsion, respiration was quickly resumed, and no arrhythmias were noted.

*Recent Myocardial Infarction.*—Two patients with recent myocardial infarction were also given electroshock therapy. One was a 39-year-old white man who

had sustained a posterior infarct six weeks previously. Residual changes consisted of a deep $Q_3$, negative $T_3$, and flat T in Lead $V_8$. Immediately following a grand mal seizure, the record changed, in that $T_3$ transiently rose to become low-positive. The electrocardiogram of a 52-year-old white woman showed a small $Q_2$ and sharply negative $T_2$ and $T_3$ as residua of a posterior infarct several months previously. There was apparent improvement after the convulsion, with $T_2$ becoming positive and $T_3$ flat. In both instances the duration of the changes was only three to five minutes.

## DISCUSSION

An increase of electrocardiographic abnormalities has been observed during intense emotional stress and during psychiatric disorders, and has been attributed to autonomic nervous system imbalance. Mainzer and Krause[15] reported pathologically changed tracings during fear of impending operation in twenty-nine of fifty-three patients. Logue, Hanson, and Knight[16] showed variations from normal in 49 per cent of 150 patients with neurocirculatory asthenia, but felt that there was no characteristic electrocardiogram in this condition. Wendkos[17] demonstrated that T waves in precordial leads in emotionally unstable persons may vary from the normal on the basis of increased sympathetic or parasympathetic tone. Heyer, Winans, and Plessinger[18] found electrocardiographic abnormalities in psychotic patients increased to an incidence of 21.5 per cent, as compared to 3 per cent in controls.

In this series, we are reasonably certain of each diagnosis of organic heart disease, since clinical findings were correlated with the electrocardiographic studies in each patient. In three patients not considered to have heart disease, there were noted increases in the P-R interval in the pretreatment tracing with no other abnormality. In each of these three patients the clinical reaction showed prolonged apnea and cyanosis and was associated with marked vagal effects on the heart. In addition, the base-line tracing of one of the fatalities showed a P-R interval of 0.22 second at a rate of 94, and the cause of death on a clinical basis was considered to be cardiac arrest. It is thus suggested that prolongation of the P-R interval may indicate vagotonia and predispose to untoward post-treatment reactions.

Silfverskiöld and Amark[19] in 1943 reported the venous pressure to rise to high values during the tonic phase of the convulsion and to decline gradually during the clonic phase. Arterial pressures likewise increased greatly during the convulsion. Altschule, Sulzbach, and Tillotson[20] found apnea to last from the time of the stimulus to a variable period after the convulsion. They stated that during this time the patients performed the Valsalva maneuver of maximal forced exspiration. The average arterial blood oxygen was found to decrease from 18.83 volumes per cent before the convulsion to 12.86 volumes per cent immediately after, the average pH of arterial blood decreasing from 7.445 to 7.142.

Even in the patients with no evidence of heart disease, the incidence of arrhythmias following the convulsions in this series is considerably higher than that reported in previous studies. One reason for the difference may be that more

abnormalities were recorded because longer tracings were taken. Another possible cause for a variance in results is that all of the patients of this series had preliminary curarization, whereas most of the patients in previous reports were not given curare. Several authors have suspected curare as being a contributing or predisposing factor to untoward reactions. These results would tend to support their view. In the cases in which Prostigmine was given, we noted some improvement in respiration but little in the electrocardiogram.

Our patients with organic heart disease showed an increased susceptibility to premature contractions of atrial and ventricular origin, wandering of the pacemaker, nodal rhythm, blocked sinus impulses, and prolonged P-R intervals. Several of the rhythm disorders were potentially dangerous, such as sinus standstill of two to three seconds on several occasions and runs of rapid premature ventricular contractions. A fatal outcome could be the result of cardiac arrest in such cases, or of ventricular fibrillation superimposed on this condition or developing as a complication of paroxysmal ventricular tachycardia. Since myocardial damage appears to predispose to arrhythmias, there is a greater risk of treatment in such patients.

*Theoretical Considerations.*—Previous investigators[9, 12] ascribe the postconvulsive arrhythmias to a hyperactivity of the vagus; this is borne out by the disappearance of most of them following adequate atropinization. The reflexes bringing about increased vagus tone probably have their origin in the changes in the respiratory and cardiovascular systems immediately following the convulsion. A lowered blood pH following the convulsion accentuates the vagal effects, as acidosis potentiates the inhibitory effects of acetylcholine.[21]

The increase in cardiac rate during the tonic phase of the convulsion appears to be due to the increased sympathetic tone which is a response to the muscular activity. Direct stimulation of the sympathetic centers may well contribute. The changes in rhythm during petit mal responses are most likely the result of direct central autonomic stimulation, and this, in addition, is a factor in some of the postconvulsive arrhythmias. The evidence for such an origin of cardiac arrhythmias recently has been excellently summarized in an editorial and experimentally demonstrated by Weinberg.[22] It has been shown that stimulation of cardiac sympathetic nerves in lightly anesthetized cats can cause ventricular extrasystoles and ventricular tachycardia.[23] Disturbances of rhythm have been noted following air encephalograms.[24]

An increased irritability of the myocardium due to anoxia and to increased cardiac work is another potential cause of arrhythmias. The increased incidence of abnormalities of rhythm in patients with myocardial damage supports the idea of a local origin caused by myocardial irritability.

A transitory rise in the height of the P waves and depression of the RS-T segments were most frequently noted in Leads II and III, but also occurred in Lead I. They can be explained by the marked increase in the venous return after the sudden cessation of the forced expiratory maneuver, which pools the venous blood in the periphery. A resulting dilatation of the right atrium and overloading of the right ventricle would account for such electrocardiographic changes.

Many of our electrocardiograms showed a temporary elevation of T waves in all leads. In eleven patients with electrocardiographic abnormalities, the immediate post-treatment tracings appeared considerably improved because of this change. Two of our patients with residua of posterior myocardial infarctions showed temporary reversal of negative T waves. Anoxemia and increased muscular exertion would be expected to produce lowering or negativity of the T waves in patients with coronary insufficiency and depression of the RS-T segments. Similar adverse changes may occur in normal persons under stress; they were also described in a study of the electrocardiogram in insulin shock.[25] Electrolyte changes seem the most likely explanation of the occasionally striking T-wave elevations. Acidosis produces significantly taller T waves,[26] and a lowering of the blood pH is known to occur immediately after the convulsion. A release of potassium from the interior of injured muscle cells may be responsible. However, potassium does not make erect the inverted T waves of myocardial infarction, but tends to invert it further.[27]

*Conclusions as to Value of Pretreatment Medication.*—Only preliminary studies have been done in pretreatment medication in order to avoid complications of therapy. Quinidine therapy in selected cases has been previously recommended by Hayman.[28] Quinidine would seem to be indicated for prophylaxis in patients showing premature ventricular contractions in the pretreatment electrocardiogram. Quinidine sulfate in small doses, orally, has proved effective in three of our cases in reducing or eliminating frequent premature ventricular contractions after the convulsion. Prompt administration of oxygen is also a most worthwhile procedure in such cases.

Atropine has been very effective in eliminating alarming cardiovascular and respiratory reactions in a small group of cases. Bellet and associates[9] noted the disappearance of postshock arrhythmias in three cases in which atropine was given to evaluate the role of increased vagal tone. Larragoiti[29] advised its use in vagotonic patients with a history of "vagal crises" and in prolonged apnea. He also administered atropine in combination with Aminophyllin to patients with coronary disease. We have learned that to obtain the desired effect, atropine must be given in adequate doses, from 1.3 mg. (grain 1/50) to 2.1 mg. (grain 1/30) intramuscularly about thirty minutes before the stimulus. It acts as an effective respiratory stimulant, and long periods of postconvulsive apnea were eliminated in our cases. The usual marked vagal arrhythmias accompanying the alarming reactions were markedly reduced or eliminated by such doses, but smaller amounts were not effective. Prophylactic use of atropine seems to be of value to avoid cardiac arrest, a probable mechanism of some of the fatal reactions. Atropine has recently been found by Wilburne and associates[30] to be of value in experimental animals in preventing ventricular tachycardia, a dangerous mechanism because it may change into ventricular fibrillation and lead to death. Severe retching and vomiting during and after the treatment has been prevented by its use. The mucous membranes are made dry by its action and there is less frothing and less aspiration of mucus. Thus, there would be less chance of developing pulmonary complications.

In view of the rarity of fatal reactions, premedication with atropine is not advised routinely. However, it seems indicated to avoid complications in selected cases, and further studies are being continued in its use. Preliminary atropinization should be seriously considered whenever pretreatment electrocardiograms show prolongation of the P-R intervals, which may be the result of a "vagotonic" constitution. Arrhythmias attributed to vagal effects, prolonged apnea and cyanosis, and postconvulsive vomiting should lead to a consideration of premedication with atropine. It reduced the severity of the convulsive effects in two of our patients to a degree that treatments did not have to be abandoned, and the patients were thus enabled to get the psychiatric benefits of electroshock therapy.

## GENERAL SUMMARY

An analysis is made of electrocardiographic changes following 304 electrically induced major convulsions and twenty-three minor convulsions in 126 curarized patients. Tabulation of the disturbances of rhythm shows them to be more frequent than was previously supposed; there is an increased incidence in patients with organic heart disease.

Although no deaths were observed, some of the arrhythmias were potentially dangerous. A postconvulsive increase in vagus tone appears to be the principal mechanism, although the local irritability of the myocardium is an additional factor.

Higher P waves and depressions of RS-T segments frequently occurred; they were apparently due to transient dilatation of the right atrium and overloading of the right ventricle after the convulsion.

A prominent elevation of T waves, probably the result of electrolytic changes, occasionally occurred and produced apparent brief improvement in the electrocardiogram.

Quinidine, given orally, and the early administration of oxygen after the convulsion have proved of value in preventing frequent premature ventricular contractions.

Adequate atropinization in selected cases shows much promise in reducing the severity of the postconvulsive apnea and cyanosis and in preventing cardiac arrhythmias. Postconvulsive vomiting has been relieved by atropine premedication, which dries the mucous membranes and reduces aspiration.

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# ON THE MEASUREMENT OF THE QRS COMPLEX AND THE INTERPRETATION THEREOF BY DIRECT AND INDIRECT DEDUCTION

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IN ANALYZING the QRS complex, the usual procedure is to measure the duration of the different components of this complex along the isoelectric line. We are of the opinion that another method of measuring is more satisfactory.

F. N. Wilson, in dividing the semidirect lead into two parts, has said, "The records actually obtained represent the algebraic sum of (1) an R wave of the kind described, written by the muscle between the exploring electrode and the ventricular cavity, and (2) a downward deflection, representing the potential variations that would occur at the epicardial surface as the result of excitation of the other parts of the ventricular wall alone."

Considering that no sharp distinction can be drawn between (1) and (2), it is difficult to use this representation as a basis for a quantitative analysis of the QRS complex.

One might, however, view the semidirect lead as the algebraic sum of the differences of potential between the exploring electrode and a point within the ventricular cavity nearest the electrode, on the one hand, and between this latter point and the indifferent electrode, on the other. The blood being a better conductor than the tissues of and outside the heart, it frequently makes very little difference where this point is located in the ventricular cavity. To avoid minor difficulties it is best, however, to select for this point a site in the ventricular cavity nearest to the exploring electrode.

The potential of the endocardial point under consideration in respect to the indifferent electrode, hereinafter termed endocardial potential, either will be negative during all of systole, or, if the septum is first heterolaterally activated, it will be positive at the start of systole and negative later.

The difference of potential between the exploring electrode and the endocardial point, hereinafter termed subepicardial difference of potential, can, however, only be positive and will be so only as long as the activating dipole layer is between these two points, with its positive side directed toward the exploring electrode. Before and after this period the potential difference will be zero.

The algebraic sum of the two differences of potential gives us the semidirect electrocardiogram. This is shown in Fig. 1.

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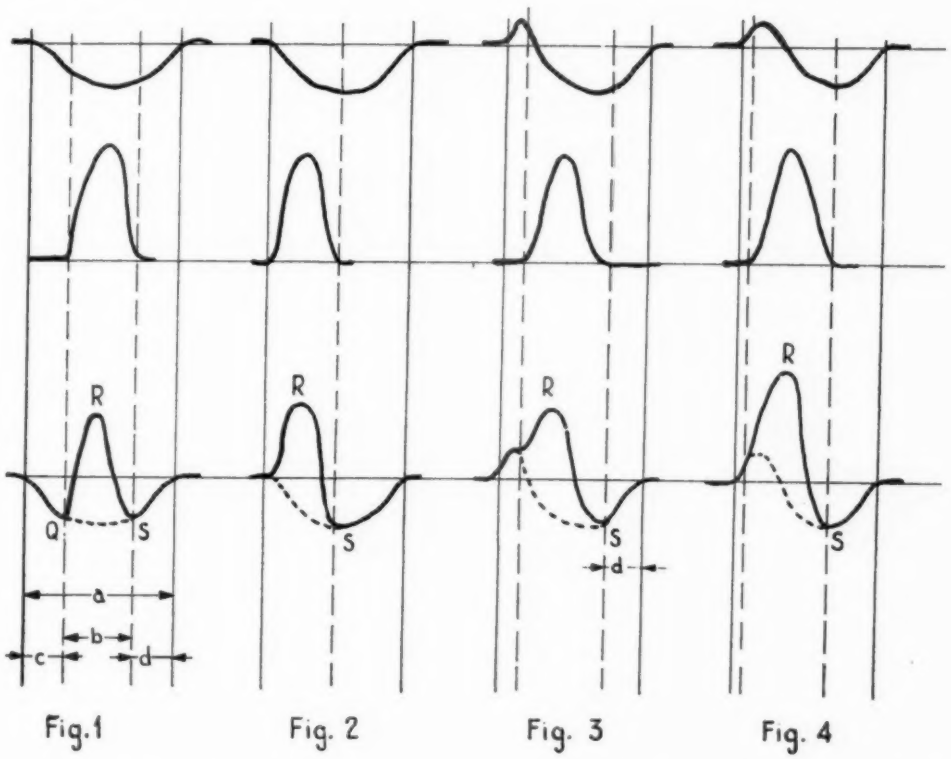
In general, the subepicardial potential difference presents a much steeper slope, as a function of time, than does the endocardial potential when it is negative, because the latter is subject to influences from all parts of the ventricular muscle more or less dispersed in time (see Appendix II).

This is what enables the observer to distinguish clearly in most electrocardiograms just when the subepicardial potential difference starts to assume a positive value and when it returns to zero, that is, the length of time which the electric dipolar layer accompanying the activation requires to move from the endocardial to the epicardial point. It is reasonable, therefore, when a Q is present (see Fig. 1) to measure the width of R not along the isoelectric line, but between its lowest points, that is, between the lowest point of Q and the lowest point of S, if this wave is present. The important intervals of time to measure are the total width of the QRS complex (*a* of Fig. 1), the duration of the R wave, measured at its lowest points (*b* of Fig. 1), the interval between the beginning of the QRS complex and the lowest point of the Q wave (*c* of Fig. 1), and the interval between the lowest point of the S wave and the end of the QRS complex (*d* of Fig. 1).




**Figs. 1-4.—The four graphs in the top row represent the endocardial potential as a function of time; the middle row, the subepicardial potential difference; and the bottom row, the QRS complex of a semidirect electrocardiogram. The lowest four complexes are the algebraic sum of the complexes in the two preceding rows.**

If, however, a Q wave is absent, two possibilities exist. Either the wall of muscle between the exploring electrode and the endocardial point is activated from the very beginning (Fig. 2), or the septum is first activated heterolaterally (Figs. 3 and 4). In actual practice these two possibilities are often difficult to distinguish (compare Fig. 2 and Fig. 4). If, however, the ascending limb of the R wave shows a notch anywhere (Fig. 3), this will sometimes clearly indicate the moment when the activation of the interjacent muscle wall begins,* as is seen frequently in cases of right bundle branch block.

Beside the logical connection which it has with the production of the various parts of the electrocardiogram, our method of measuring possibly has the further advantage of its results being quantitatively less dependent on the apparatus employed, for the moment at which the deflection begins to move in another direction is surely less affected by the inertia of the apparatus than the moment at which the zero line is crossed.

In a normal semidirect electrocardiogram of the QRS complex, the interval indicated by *a* of Fig. 1 measures the time needed to activate the whole of the ventricular muscle; that indicated by *b* of Fig. 1, the time needed for the activating dipole layer to move from the endocardial surface outward through the muscular wall to a point just beneath the exploring electrode; and that indicated by *c* of Fig. 1 measures the time between the beginning of activation of the ventricular muscle and the beginning of activation of that portion of the muscle wall between the exploring electrode and the endocardial point which has been referred to. The duration of the interval shown in *d* of Fig. 1 indicates the time that elapses between the completion of the activation of the subepicardial point beneath the exploring electrode and the completion of the activation of the entire ventricular muscle.

We shall now investigate what determines the duration of the endocardial curve and the subepicardial curve.

*Duration of Endocardial Curve.*—Many factors combine to determine the duration of the endocardial curve: the rate of conduction through the Purkinje tissues, the length of the latter, the thickness of the cardiac muscle, and the rate at which the dipole layer is propagated through the ventricular muscle.

The rate of propagation through the Purkinje tissues is roughly 4.0 meters per second and the maximum length of these tissues (the inflow tract of the left ventricle, or the distance from the mitral valve to the apex) is about 70 millimeters. Hence, if the inflow tract is lengthened by 100 per cent, the time needed to pass along is increased by 17.5 milliseconds. The rate of propagation of the dipole layer is much lower, about 0.4 meter per second. If the thickness of the cardiac muscle is 7 millimeters and it becomes twice that, then the time needed for the dipole layer to pass through will be increased by 17.5 milliseconds. Both increases in time are important and lengthen the endocardial curve appreciably.

It is to be expected that under abnormal conditions, such as ischemia or fibrosis, a change will take place in the rate at which the dipole layer is propagated through the cardiac muscle. Unfortunately, our knowledge regarding these changes of rate is still insufficient.

*Not every notch on the ascending limb of the R wave is the result of such activation.

*Duration of Subepicardial Curve.*—The duration of the subepicardial curve is determined by two factors: the thickness of the cardiac muscle and the rate at which the dipole layer is propagated through this muscle.

If in the semidirect electrocardiogram we find a lengthening of the subepicardial curve of about 10 milliseconds and if the same is observed in various parts of the ventricle, there is very probably a thickening of the cardiac muscle. If the activation of this group of muscles is the last to be completed, then the endocardial curve will also be longer, for a local thickening of the cardiac muscle practically never occurs.

A local lengthening or shortening of the subepicardial curve indicates, therefore, a local change in the rate of propagation in the cardiac muscle.

If in a semidirect electrocardiogram there occurs a lengthening of the endocardial curve by about 10 milliseconds without there being a lengthening of the subepicardial curve, then we are dealing with dilatation of the heart or with slowed conduction in the Purkinje tissues. When conduction in these tissues is deranged, other changes often occur in the electrocardiogram and these sometimes facilitate further analysis. Furthermore, a pronounced dilatation of the ventricle can naturally be determined by x-ray examination.

There are many possible combinations, but we shall not enter into this subject in detail here. We may perhaps merely point out that the duration of the interval indicated in *d* of Fig. 1 determines the moment at which the subepicardial point is activated; when this interval is large this point is activated early; when it is small the activation is late.

## SUMMARY

A new method of measuring the QRS complex is suggested. This method supplies data with regard to the condition of the cardiac muscle which so far it has been impossible to obtain.

## APPENDIX I

The length of the interval *a* of Fig. 1 is dependent on many factors. Hence, the first thing we determine is the length of the interval *b* of Fig. 1. For this purpose we usually use Lead $V_5$.

Electrocardiograms were made of 102 patients in all, and the results were as follows: In eighty-one cases the length *b* was less than 64 milliseconds, in twenty-one it was longer than 64 milliseconds, and varied between 64 and 100 milliseconds. On clinical grounds it may very probably be assumed that seventeen of the latter group of patients were suffering from hypertrophy of the left ventricular muscle. In two cases hypertrophy was a possibility; in the remaining two, hypertrophy of the left ventricular muscle was unlikely.

## APPENDIX II

*The Origin of Endocardial Potential and of Subepicardial Potential Difference.*—Let us imagine the ideal case of a heart consisting of one chamber only, enclosed on all sides by a wall, the openings in which are so small as to be negligible, and,

furthermore, let us imagine that at a given moment this wall, over its entire inner surface, is completely occupied by a dipole layer with a constant dipole density per square centimeter of $\mu$. Let us suppose also that this dipole layer, without change of dipole density, works its way outward through the wall and reaches simultaneously its entire outer surface and then suddenly disappears.

Under the influence of this dipole layer, no difference of potential would then arise between the epicardial point and the indifferent electrode. As long as the dipole layer was in existence, the endocardial potential would be just $-4\pi\mu$ in electrostatic centimeter-gram-second units, but in a direct lead this would be exactly neutralized by the subepicardial potential difference, which would then be $+4\pi\mu$. This would be the case because the direct lead is equal to the difference between the endocardial potential and the epicardial potential.

A real heart, however, consists of two chambers with large openings and all parts of the surface of its walls are not activated at the same time. Hence, if only a small portion of the wall is occupied by a dipole layer, the endocardial potential will be only slightly negative, even immediately beneath the particular bit of the activated wall. The endocardial potential will not be greatly influenced by the position of the endocardial point; the subepicardial potential difference is, however, very greatly dependent on the position of the epicardial point with respect to the dipole layer.

As a result of the various parts of the wall being activated successively, the endocardial potential will show a relatively flat curve and will remain less than $-4\pi\mu$, unless one ventricle, or both ventricles taken as a whole, should happen to be surrounded on all sides by the uninterrupted dipole layer. In this connection an average value for $\mu$ should be taken.

Quite different is the behavior of the subepicardial potential difference. As long as there is no dipole layer between the endocardial and epicardial points, the potential difference between the two will vary little from zero. As soon, however, as a dipole layer comes into being between these points or a neighboring dipole layer extends so as to lie between them, a potential difference between these points will arise comparatively suddenly, the difference amounting to from $2\pi$ to $4\pi \times$ dipole density per square centimeter in that spot.

# Clinical Reports

## MORGAGNI-ADAMS-STOKES ATTACKS CAUSED BY TRANSIENT RECURRENT VENTRICULAR FIBRILLATION IN A PATIENT WITHOUT APPARENT ORGANIC HEART DISEASE

A Case Report

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VENTRICULAR fibrillation was assumed to be a very probable cause of sudden death in man by MacWilliam[27] as early as 1889, long before the introduction of the electrocardiograph in clinical practice. He reached this conclusion after studying experimentally induced ventricular fibrillation in animals. In 1850, Hoffa and Ludwig[15] had been able to demonstrate that faradization of the heart of animals led to ventricular fibrillation and death. In 1912, Robinson[36] recorded electrocardiographically short periods of ventricular fibrillation in two patients after clinical death. The duration of the disturbances in the two patients was four and one-half and twenty minutes, respectively. Three years later, Halsey[11] reported a longer attack of terminal ventricular fibrillation. Since then, many cases of terminal ventricular fibrillation have been described.[13,18,28,48] The correctness of MacWilliam's assertion has, therefore, been proved.

Transient attacks of "well established ventricular fibrillation" were recorded for the first time by Robinson and Bredeck[37] in 1917. The patient had repeated Adams-Stokes attacks and pronounced cardiac insufficiency, and died thirty hours later during another episode of fibrillation. Since this observation a number of other cases of transient ventricular fibrillation have been reported.[7,9,10,17,20,21,29,32,33,39,40-47,56,57]

It appears from the reports that the cause of both the terminal and the transient form of ventricular fibrillation is always to be found in association with organic disease of the heart, most often coronary sclerosis or thrombosis with infarction. Frequently there is also present complete A-V heart block.[5,7,9,10,20,32,33,39,40,47,56]

From Krohgstøtten Hospital, Oslo, Norway.
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It has not been possible to find any report of an electrocardiographically verified case of purely functional transient ventricular fibrillation of somewhat long duration. As early as 1911, Hoffmann[17] mentioned a case of transient ventricular fibrillation which was recorded at the close of an attack of tachycardia in an apparently healthy young woman. Halsey doubted whether the brief attack of diphasic oscillations (three seconds) was really an example of ventricular fibrillation. Rasmussen[34] published an electrocardiogram which resembles one of the electrocardiograms (Fig. 4) obtained from our patient immediately before the attack of ventricular fibrillation. It presented a succession of ventricular extrasystoles, which is the pathognomonic precursor of ventricular fibrillation. Rasmussen's patient did not faint during this attack, which lasted only two and one-half seconds, but later he had several Adams-Stokes attacks. It is probable that during these syncopal attacks well-developed ventricular fibrillation was present, but the attacks were not recorded. As in Hoffmann's case, no organic heart disease was discovered in Rasmussen's patient. A case described by Bjerlöv[1] in 1932 as an example of ventricular fibrillation with recovery has since been considered by Öhnell[59] to have been an example of the Wolff-Parkinson-White syndrome with paroxysmal tachycardia. Between the attacks of tachycardia the electrocardiogram always showed bundle branch block and a short P-Q interval. Öhnell has reported a case of Wolff-Parkinson-White syndrome with a similar electrocardiogram.[58]

The case which is to be reported is believed to be the only case of ventricular fibrillation of functional origin that has been recorded electrocardiographically (Fig. 1).

## CASE REPORT

An engineer, 38 years of age, was admitted to the Krohgstøtten Hospital because of attacks of syncope. The past history was not significant; he had not had rheumatic fever or chorea. He had had no cardiovascular symptoms until the spring of 1943 when he began to notice attacks of palpitation. Even after this symptom developed, he had no shortness of breath, chest pain, or edema. The attacks of palpitation seemed to be made worse by smoking. They were not related to exertion; indeed, he was more conscious of the disturbance when he was at rest. After the attacks of palpitation had been present for one month, he consulted a physician, who discovered nothing on clinical or radiological examination of the heart; electrocardiograms were not taken at this time.

The attacks of palpitation were always quite transient until January, 1944, when they became more frequent and more prolonged. On the evening of Jan. 24, 1944, the patient fainted while sitting at his desk in his home. Observers estimated that he was unconscious for approximately two minutes. On the next evening he fainted while working at his desk at his place of work. After four attacks of syncope during the morning of Jan. 26, 1944, he was admitted to the hospital.

On admission he was perspiring, his skin was cold, and he looked ill. However, he stated that he had felt well before and after the attacks. While being initially examined, he had three or four syncopal seizures. Between attacks the pulse rate was 70 to 90 per minute. The rhythm was quite irregular because of isolated extrasystoles or short runs of extrasystoles. In the beginning of an attack it was observed that the pulse and heart sounds became imperceptible for eight to ten seconds; fainting then occurred, but the only suggestion of a convulsion was the presence of slight twitching of the leg muscles immediately after one attack. There was no vomiting or incontinence during the attacks. At the initial examination, electrocardiograms were taken immediately before, during, and after an attack.

The first group of four simultaneous tracings (Fig. 1) shows at its beginning a normal sinus rhythm with a rate of 70 per minute. There then appears a run of approximately ten deformed ventricular complexes which is initiated by an extrasystole This episode lasted for 2.6 seconds. Although the pulse could not be felt and the patient felt "a little queer," he did not lose consciousness. The next group of four simultaneous tracings shows extrasystoles, at first singly, and later in short runs. The continuous electrocardiogram at this point was stopped. A few seconds later, the patient became unconscious and the electrocardiogram in the third group of tracings was recorded (Lead I and Lead II). During this period of ventricular fibrillation, the ventricular complexes are sometimes fairly regular but the shape of the waves differs considerably. No P waves can be seen. This episode of ventricular fibrillation lasted 17.7 seconds. The ventricular rate was 360 per minute at the beginning and 390 per minute at the end of the attack. At the end of the attack of fibrillation, a slow sinus rhythm is present. After two cycles of this mechanism, the P waves disappear, possibly as a result of the onset of nodal rhythm.

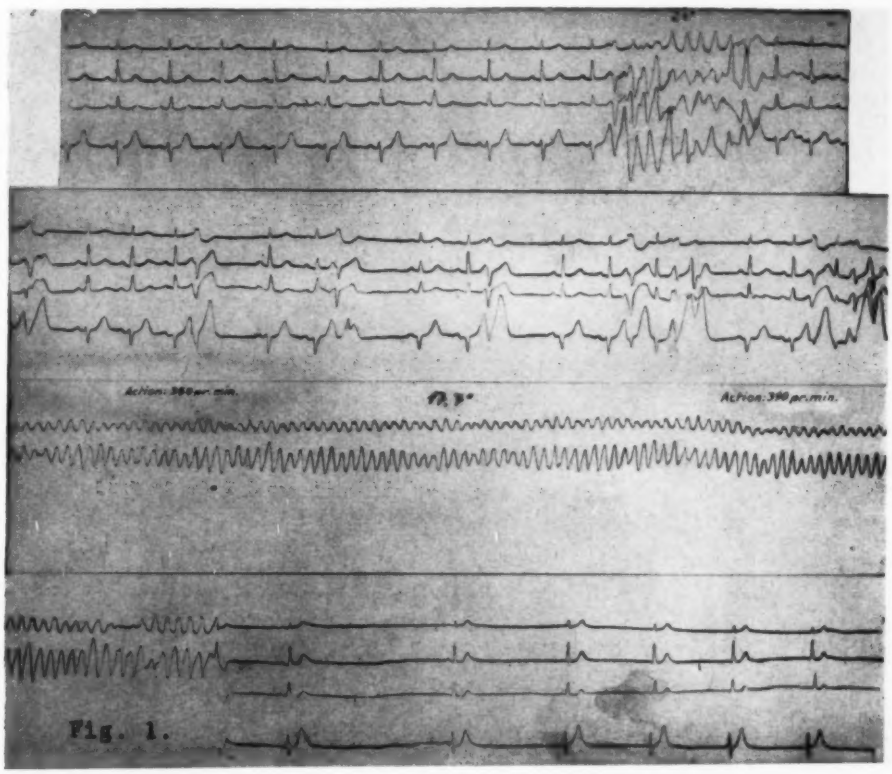


Fig. 1.—After a period of sinus rhythm followed by a number of deformed ventricular complexes, electrocardiogram shows ventricular fibrillation and then sinus bradycardia and A-V nodal rhythm. The different parts of the electrocardiograms are continuous except for some seconds just before the patient developed the Adams-Stokes attack. When he fainted the electrocardiogram was immediately resumed.

During the period of ventricular fibrillation, no pulse was perceptible and respiration ceased. The tracing which was made during this attack and which has just been described was not available to us for two hours. Before we saw the recorded tracing, the patient was given 1.0 ml., and after one-half hour, an additional 0.75 ml. of adrenaline, subcutaneously, as the attacks recurred. When the electrocardiogram was available and the mechanism observed, the patient

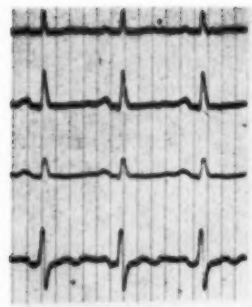

Fig 2.

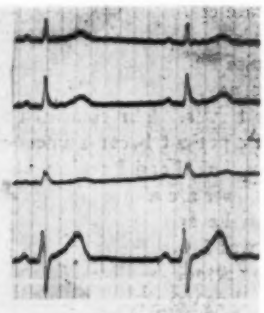

Fig. 3.

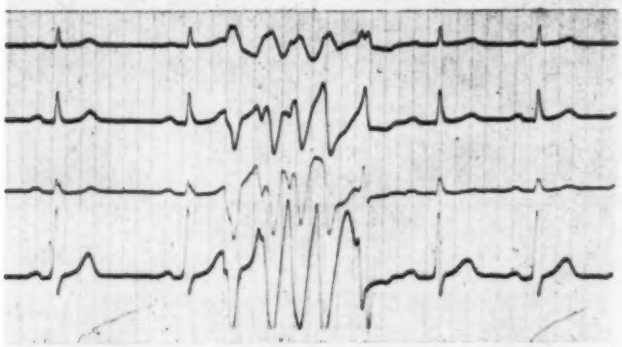

Fig 4.

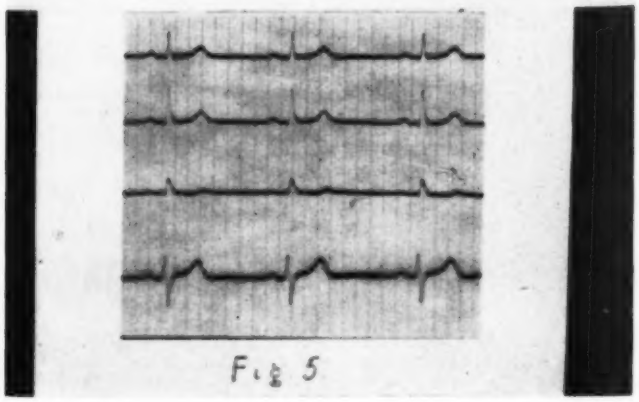

Fig 5

**Fig. 2.**—The electrocardiogram taken the day after the attack illustrated in Fig. 1 shows flattened T waves in the standard leads.

**Fig. 3.**—A normal electrocardiogram taken two days after the attack illustrated in Fig. 1.

**Fig. 4.**—At a control examination one week after the attack the electrocardiogram shows a brief run of extrasystoles.

**Fig. 5.**—Electrocardiogram taken three years after the attack is quite normal.

was given 0.20 Gm. of quinidine sulfate by mouth. At the end of four hours, he had received, in all, 0.60 Gm. of quinidine sulfate. At this time the syncopal attacks ceased, though the patient noticed occasional extrasystoles. Within seven hours after the electrocardiogram was taken, he had received, altogether, 1.0 Gm. of quinidine sulfate.

On the day of admission, before the heart was brought under the influence of quinidine, the patient had, in all, ten attacks of syncope. The shortest attack lasted 17.7 seconds (the attack shown in Fig. 1) and the longest attack lasted for some seconds over two and one-half minutes. On the day after his admission he received, in all, 1.0 Gm. of quinidine by mouth. Thereafter, he continued to receive 0.20 Gm. of quinidine orally per day.

It will be noticed that the T waves shown in Fig. 1 are normally upright. A tracing taken two days after admission (Fig. 2) shows the T waves to be flattened in the indirect leads. A tracing taken two days later (Fig. 3) is quite normal.

During his hospital stay, studies other than electrocardiographic observations were normal. The blood pressure on several occasions was 120/80. Radiographic studies of the heart showed no abnormality. The hemoglobin, red and white blood cell counts, and the differential count were normal. The erythrocyte sedimentation rate was 4.0 mm. in one hour. The serum cholesterol was 110 mg. per cent. On the evening of admission the patient had a slight temperature, but thereafter he was afebrile. He remained in the hospital for a fortnight and was discharged in good health. He was directed to take 0.20 Gm. of quinidine three times a day.

One week after he had been dismissed from the hospital he was re-examined. He had been entirely free of symptoms except for consciousness of occasional extrasystoles. However, a tracing taken at this time (Fig. 4) did record a run of five extrasystoles. At the patient's express request, he was allowed to discontinue quinidine. Three months after discontinuing the drug, he was again admitted to the hospital because of recurrence of syncopal attacks. During this second hospital admission, we did not succeed in recording any attacks of ventricular fibrillation electrocardiographically. The patient was then discharged on 0.10 Gm. of quinidine sulfate, orally, twice a day; this was subsequently reduced to 0.10 Gm. once a day. The patient has been re-examined twice and has continued to be entirely free of symptoms except for a very occasional extrasystole. The small dose of quinidine has been continued. An electrocardiogram (Fig. 5) made Jan. 5, 1947, almost three years after his original admission, is entirely normal.

## DISCUSSION

Two other disturbances of rhythm are so frequently associated with the development of ventricular fibrillation that it is difficult to avoid the conclusion that these disturbances have a causative relationship to ventricular fibrillation. One is ventricular extrasystolic disturbances and the other is complete A-V heart block.

Increased impulse formation due to ventricular extrasystoles has been frequently observed to precede the onset of ventricular fibrillation. Schwartz[39] has stated that if in a patient with complete A-V heart block there is observed an increase in the basal ventricular rate (for example, from 38 to 65 per minute) due to an extrasystolic disturbance, subsequent syncope in such a patient can be assumed to be the result of the occurrence of ventricular fibrillation.

The importance of complete A-V heart block in the development of ventricular fibrillation has been particularly emphasized by American authors.[7,9,10,20,32,33,39,40,47,56] Davis and Sprague[6] hold that A-V heart block is the pathogenetic basis for the occurrence of ventricular fibrillation and that it is the improvement in A-V conduction that brings the fibrillation to an end. Theoretically, say these authors, one might expect an eventual "circus move-

ment" in the ventricle to be interrupted by the excitation wave from the auriculoventricular node. Rasmussen[35] produced ventricular fibrillation experimentally in exposed hearts of dogs by clamping the pulmonary artery and the aorta. The longer the clamp was applied, the longer became the P-R interval until, finally, complete A-V block developed. The latter was soon followed by either ventricular fibrillation or ventricular standstill.

Ventricular fibrillation is, therefore, not only dependent upon impulses of high frequency from one or more centers, but also upon disturbances of conduction. In brief, several factors seem to be required to bring about ventricular fibrillation. There usually exists serious organic disease of the heart, such as coronary sclerosis or coronary thrombosis with infarction. The anoxia that ensues leads to greatly increased irritability of the ventricles; then, if for the same reason conductional disturbances arise, especially complete A-V block, ventricular fibrillation may easily be evoked as a result of the absence of the normal excitation wave that would have rendered the ventricles refractory.

In an organically sound heart with no disturbance in the conducting system it seems to be very difficult for ventricular fibrillation to develop. Wiggers[54,p.537] believes that when it does arise, recovery is rare in man and in other large animals. The heart of the smaller animal (rat, cat) is more likely to recover spontaneously.

Ventricular tachycardia of functional origin has been recorded by several investigators,[6,8,21] but well-established functional ventricular fibrillation has not been recorded in man. In our case no organic heart disease existed nor any form of heart block. Thus, it seems that impulses of high frequency are alone sufficient to evoke ventricular fibrillation.

A feature of particular interest is the fact that the attacks continued during the administration of adrenalin and were unaffected, apparently, by this drug. It is likewise remarkable that the patient survived so many seizures, sixteen in all. This again shows that an organically sound heart can withstand numerous attacks of ventricular fibrillation.

Several authors[7,8,51] have pointed out that the T waves become negative after ventricular paroxysmal tachycardia and ventricular fibrillation. In our case there was no change in the T waves immediately after the seizures (Fig. 1). Not until the next day (Fig. 2) did the T waves become flat in the three standard leads and diphasic in Lead IV. Two days later the electrocardiogram (Fig. 3) was completely normal.

When a case of Adams-Stokes disease is being considered, complete A-V heart block with ventricular standstill usually is thought of first as the responsible mechanism. It is now held by several authors[16,32,33,38,57] that Adams-Stokes attacks are equally often, or even oftener, the result of ventricular tachycardia or ventricular fibrillation.

*Treatment.*—Quinidine sulfate, by mouth, is generally recognized to be an effective remedy in treatment of ventricular paroxysmal tachycardia and paroxysmal ventricular fibrillation. However, cases have been reported in which ventricular fibrillation has been evoked by the use of quinidine. This has occurred especially where there existed a serious myocardial lesion secondary to

coronary thrombosis and where the conduction system was damaged with resulting complete A-V heart block. Quinidine reduces all of the functions of the cardiac muscle. If quinidine has a greater effect in prolonging the conduction time than in prolonging the refractory period, it will be more likely to evoke rather than to prevent or put an end to ventricular fibrillation.

Kerr and Bender[20] believed that quinidine sulfate was the cause of ventricular fibrillation in their case. Davis and Sprague[5] presented a similar case, in which, however, the patient had also been given digitalis which may have been a contributory factor. Schwartz and Jezer[45] gave small doses of quinidine sulfate, intravenously, to two patients with A-V block, who then developed transient attacks of ventricular fibrillation. They believe, therefore, that quinidine, given by mouth, may also evoke ventricular fibrillation in susceptible patients. Jervell[18] reported two cases of cardiac infarction with ventricular paroxysmal tachycardia in which quinidine was given intravenously. One of the patients collapsed, but afterward recovered. The other died immediately after the injection.

White[53] has stated that there have sometimes been seen strikingly good effects from intravenous injection of quinidine sulfate, but that it is simpler, safer, and probably equally effective to administer this drug orally. It has been reported by Brinchmann[4] that large doses of quinidine have been given by mouth for several years without injurious effects. In only exceptional cases does quinidine, given orally, induce ventricular fibrillation.

Levine[23] showed in experiments on cats that quinidine prevented the onset of ventricular fibrillation by increasing the refractory period. He, therefore, finds it rational to use quinidine in ventricular fibrillation. Blumenthal and Oppenheimer[2] showed by experiments that quinidine renders the heart refractory to substances that bring on ventricular fibrillation.

As in experiments on animals, the good effects of quinidine in patients with ventricular tachycardia and ventricular fibrillation is most probably due to the fact that prolongation of the refractory period is the predominant effect of the drug. Even though given in small doses (0.20 Gm., by mouth, five times in seven hours) quinidine in our case is believed to have prevented recurrence of the attacks. After the last attack our patient has been taking 0.10 Gm. of quinidine sulfate by mouth, daily, and has had no attack for three years.

## SUMMARY

1. The case of a healthy young man who had numerous Adams-Stokes attacks is presented. An electrocardiogram recorded during an attack which lasted 17.7 seconds showed typical ventricular fibrillation. The longest attack lasted some seconds over two and one-half minutes. Since the patient has shown no evidence of organic heart disease over a period of three years, it is believed that the ventricular fibrillation must have been of purely functional origin.

2. The pathogenesis of ventricular fibrillation is briefly discussed: both hyperirritability of the ventricles (ventricular extrasystoles) and complete A-V

heart block must be present in almost all cases in order that ventricular fibrillation develop. In some instances, as in the presented patient with an apparently sound heart, hyperirritability may be sufficient to produce ventricular fibrillation.

3. The use of quinidine for treatment of ventricular fibrillation is discussed. In the author's case it is probable that quinidine, administered by mouth, prevented recurrence of the attacks.

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# TUBERCULOUS FALSE ANEURYSM OF THE ABDOMINAL AORTA WITH RUPTURE INTO THE STOMACH

## A Case Report with Review of the Literature

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TUBERCULOUS mycotic aneurysm of the aorta is a rare condition. In 1944 Owens and Bass[1] reported an instance of this condition occurring in the abdominal aorta and reviewed the twenty-one such cases published previously. In all of these twenty-one cases the aortic lesion had resulted from involvement of its wall by an adjacent tuberculous lymph node and this was apparently the mechanism in the case to be presented in this paper. In the case reported by Owens and Bass[1] and in the unpublished case of Brooks and Dawson,[2] the aneurysm, which was thoracic, had resulted from hematogenous tuberculous infection of the aortic wall. The latter named case is noted because of its similarity to the former in spite of its location above the diaphragm. No adjacent tuberculous lymph nodes were found at autopsy in these patients and acid-fast bacilli were demonstrated in the aortic lesion.

The case of Brooks and Dawson[2] was that of a 45-year-old man, admitted for intense continuous epigastric pain and vomiting of small amounts of bright blood. He died two days later, after massive hematemesis. Autopsy showed fibrocaseous tuberculosis of the upper lobes of both lungs, a tuberculous false aneurysm of the descending aorta which had ruptured into the esophagus, acid-fast bacilli in the wall of the aneurysm, and several mediastinal nodes containing small tuberculous lesions, none of which had ruptured into the aorta. This case and that of Owens and Bass are primary mycotic aneurysms, as defined by Crane,[3] that is, "a lesion developing in the wall of an artery, which is not associated with any demonstrable intravascular inflammatory focus, as bacterial endocarditis, or with any in the surrounding tissue." The instance of tuberculous aneurysm to be presented here, like those previously reported, while mycotic, is not primary in this sense since the aortic lesion was an extension from an adjacent tuberculous area.

The stomach is not a common site of rupture of aortic aneurysm. Rottino[4] in 1943 reviewed thirty-one reported cases of abdominal aortic aneurysm which had ruptured into the gastrointestinal tract. Hunt and Weller[5] in 1946 supplemented Rottino's report by including a case of their own and bringing the number

From the Good Samaritan Hospital, Lexington, Ky.
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TABLE I. CLINICAL AND PATHOLOGIC FINDINGS IN THE CASE BEING REPORTED AND IN THREE CASES WHICH WERE EITHER OMITTED FROM OR OCCURRED SINCE LAST REVIEW

| CASE | DATE | AUTHOR | AGE | SEX | PERTINENT HISTORY LEADING TO ADMISSION | CLINICAL OBSERVATIONS | COURSE | PATHOLOGIC FINDINGS |
|---|---|---|---|---|---|---|---|---|
| 42* | 1931 | Bogazzi[6] | 70 | M | Hematemesis and melena | Profound anemia and emaciation; epigastrium tender and resistant | Death four days after admission following continued hemorrhage by bowel | Tuberculous false aneurysm of the aorta; rupture into the duodenum; erosion through tuberculous lymph node; tuberculous infiltration of adventitia and media of aorta, of duodenal wall, of bodies of three lumbar vertebrae, and of lungs with cavitation |
| 43 | 1947 | Balice[7] | 31 | M | Attacks of intense epigastric pain | Exploratory operation revealing pulsating mass behind stomach; serologic tests for syphilis equivocal; penile sore, 20 years of age | Readmission six weeks after operation; gross hematemesis and death in a few hours | Aneurysm 7.0 × 3.5 × 3.0 cm. arising from aorta between superior and inferior mesenteric arteries; rupture into third portion of duodenum; hyalinization and fibrosis of wall with perivascular round cell infiltration |
| 44 | 1947 | Cleland[8] | 65 | F | Collapse and profuse hematemesis | Pulsating tumor in epigastrium; psychosis; Wassermann of blood and spinal fluid negative | Six days after first hematemesis, epileptiform seizure followed by gross hematemesis and death | Aneurysm of aorta 3.7 cm. in diameter; aorta 3.0 cm. above bifurcation with adhering duodenojejunal junction; rupture into jejunum; extensive atheroma |
| 45 | 1948 | Scott, Grimes, and Maxwell | 49 | M | Profuse hematemesis | Subtotal gastrectomy, after equivocal x-ray findings, with recovery; serologic test for syphilis negative; no evidence of ulcer in operation | Readmission six days after discharge on account of abdominal pain; hematemesis repeated with death twelve days after readmission | Localized tuberculous aortitis; false aneurysm 3.0 cm. in diameter arising from aorta just above celiac axis with rupture into stomach 2.0 cm. below esophageal ostium; stomach adherent to aneurysm; scarred lung apices; caseous tracheobronchial lymph node; miliary tuberculosis of liver and spleen |

*Numbered in sequence with cases reported by Rottino[4] and Hunt and Weller.[5]

to forty-one. Of these only five had ruptured into the stomach. Bagozzi's[6] case, reported in 1931, was omitted from these two reviews. It was an instance of rupture of a tuberculous false aneurysm into the duodenum. The type of aneurysm resembled closely the one to be presented here. It is tabulated with two others reported since Hunt and Weller's review[5] (Table I). These with the case to be presented here bring the total to forty-five, only six having ruptured into the stomach. Thirty-five had ruptured into the duodenum, three into the jejunum, and one into an unspecified portion of the small intestine.

The frequency of rupture into the duodenum is probably dependent on the anatomic factor of relative immobility of the duodenum compared with the stomach and the small intestine. It is noteworthy that in seven of the cases of rupture into the stomach and small intestine, adhesion of the aneurysm to the viscus involved is described, as in the case to be presented. In the only two exceptions pathologic details are lacking. Quite aside from this evidence, it would appear that a necessary condition of rupture into a hollow viscus is fixation either by structure or by pathologic adhesion.

The following case is, therefore, presented because of two unusual features: its tuberculous nature and its rupture into the stomach.

## CASE REPORT

A 49-year-old white railroad machinist was admitted to the Good Samaritan Hospital, Lexington, Ky., on Dec. 5, 1945, following a gastrointestinal hemorrhage. Twenty years before admission he had had pneumonia, complicated by empyema. He had been in good health following this illness until two years before admission, at which time he had an episode of repeated vomiting and was told by his physician, after x-ray examination of his stomach, that he had a duodenal ulcer. He was placed on a bland diet which he soon abandoned. As he had no food intolerance and no further vomiting, he returned to his work. Three weeks later he vomited a large amount of blood and passed tarry stools. He was, therefore, referred to the hospital on the following day.

Physical examination revealed a well-nourished man in mild shock. His temperature was 98.6°F., pulse rate 100, respiratory rate 24, and blood pressure 95/70. The general physical examination was essentially negative. No masses could be felt in the abdomen and there was no abdominal tenderness. The erythrocyte count was 3.2 million, the leucocyte count was 7,250, and the hemoglobin was 9.7 grams per 100 c.c. of blood. A serologic test for syphilis was negative. Examination of the urine was not remarkable.

During his period of hospitalization he had no further gross bleeding and no abdominal pain. On fluoroscopic examination no abnormalities were seen in the stomach. There was a slight deformity at the junction of the first and second portions of the duodenum. The roentgenologist thought that this finding was suggestive of duodenal ulcer. An exploratory laparotomy was decided upon and he was prepared for operation by four transfusions of whole blood, with a resultant rise of the erythrocyte count to 4.0 million and of the hemoglobin to 10.8 grams. At operation (A.E.G.) on December 19, an area 1.0 cm. in diameter was noted in the serosa on the anterior wall of the duodenum which was suggestive of an ulcer. A subtotal gastrectomy was performed. This was of the Polya type and included the abnormal area of the duodenum. Examination of the portion of stomach and duodenum removed failed to show any lesion. The postoperative course was uneventful and he was discharged from the hospital on Dec. 31, 1945.

He was readmitted to the hospital on Jan. 6, 1946. For the preceding three days he had had severe, generalized, cramping abdominal pains. On examination, there was no evidence of shock. The abdomen was diffusely tender but was not rigid. There were normal peristaltic sounds. The erythrocyte count was 3.88 million and the hemoglobin was 9.4 grams.

Severe abdominal pain persisted for three days and required repeated injections of morphine for its relief. On the third hospital day he vomited a small amount of bright red blood, and following this had tarry stools. In spite of three transfusions of 500 c.c. of blood, his erythrocyte count fell to 3.0 million and his hemoglobin to 7.7 grams. On the eighth hospital day he again had severe cramping abdominal pain and vomited a large amount of dark blood containing clots. During the remainder of his hospital stay until death he had almost continuous, and very severe abdominal pain and repeated hematemeses. A Jutte tube was inserted and the stomach was irrigated with warm physiologic saline solution. Whenever the tube was unclamped dark clotted blood poured from it under considerable pressure. Four more transfusions were given but he grew gradually worse and died in shock on Jan. 18, 1946.

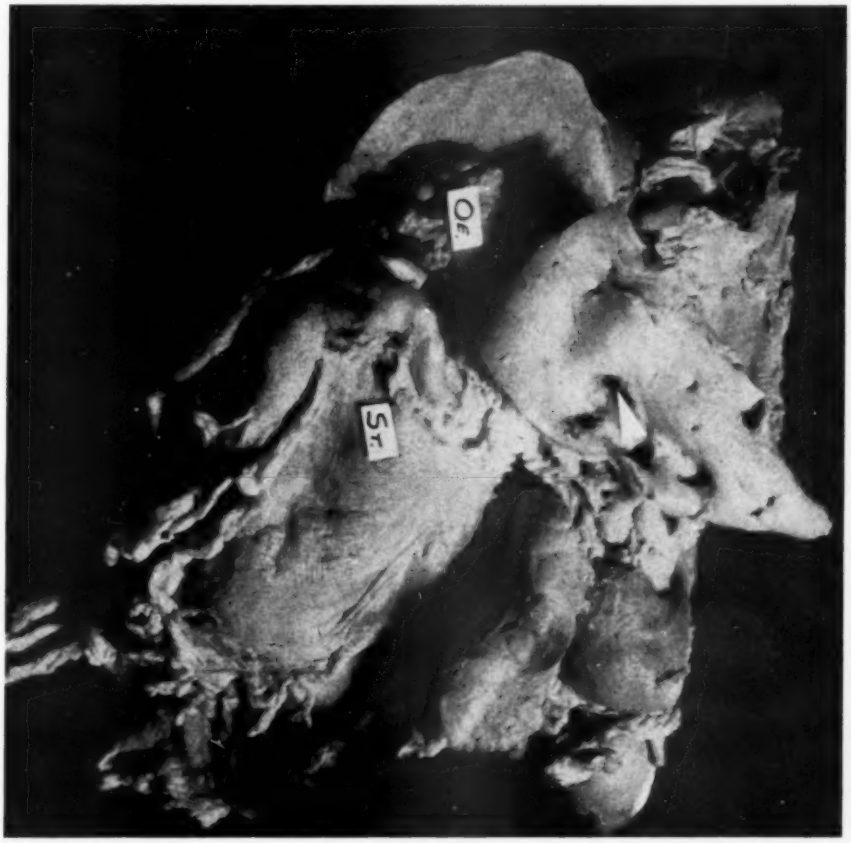


**Fig. 1.—The esophagus, stomach, and aorta viewed from their posterior aspect. The aorta has been opened. The arrow points to the point of rupture of the aorta, near the origin of the celiac axis. The aneurysmal sac lies anterior to the aorta and is hidden by it in this photograph. *OE*, esophagus; *ST*, stomach.**

*Autopsy Findings.*—An autopsy (40109-S) was performed (E. S. M.) one hour after death. The body was that of a well-developed and well-nourished white man. There was a recent, healed surgical wound in the right hypochondrium, but no other gross abnormalities were seen in the skin or subcutaneous structures. The peritoneum was smooth and glistening, showing no evidence of old or recent inflammation. The surgical wounds involving the stomach were healed. The

stomach was distended with a huge blood clot which extended into the jejunum and esophagus. No ulcer could be found in the duodenal mucosa or in the gastrojejunostomy margin.

On the posterior wall of the stomach, 2.0 cm. below the esophageal ostium, there was an opening in the mucosa measuring 7.0 mm. in diameter. Immediately adjacent to this were two smaller openings in the mucosa. These three openings were plugged with fibrin. A probe could easily be passed through these into an aneurysm measuring 3.0 cm. in diameter. The aneurysm was adherent to the posterior wall of the stomach and to the anterior surface of the aorta. An opening, 6.0 mm. in diameter, connected the lumen of the aorta with that of the aneurysmal sac. The opening in the aorta was slightly to the left and immediately above the beginning of the celiac axis. The intima of the aorta was smooth, showing very little atherosis. The aneurysm was partially filled with a laminated thrombus which was not fixed to the wall. The wall of the aneurysm measured from 3.0 to 5.0 mm. in thickness. Several small but firm lymph nodes were found in the retroperitoneal tissues surrounding the aneurysm. The findings in the aorta and stomach are shown in Figs. 1, 2, 3, and 4.


Fig. 2.—The segment of aorta has been retracted downward to reveal the aneurysmal sac (arrow) lying anterior to it. *OE*, esophagus; *ST*, stomach.

The spleen, liver, adrenals, and kidneys showed no gross lesions. The pleurae were smooth, and the lungs were dry and air containing. Old scars and emphysematous blebs distorted the apex of each lung. At the bifurcation of the trachea there was a caseous node, measuring 15 mm. in diameter. The heart was normal.

Sections from the aortic wall, the aneurysmal sac, and the stomach showed that this was a false aneurysm resulting from destruction of the aortic wall by tuberculous granulation tissue. Sections from the wall of the aorta at the opening into the aneurysm showed necrosis of the wall, with little demonstrable inflammatory changes except in the adventitia where there was tuberculous granulation tissue merging into similar tissue forming the inner wall of the aneurysmal sac. No aortic tissue could be recognized in the wall of the sac. Beyond this area of tuberculous tissue there was lymphocytic infiltration containing moderate numbers of plasma cells and eosinophilic

**Fig. 3.—The stomach, opened along its greater curvature. The point of erosion of the aneurysm into the stomach is indicated by the arrow. The gastrojejunal anastomosis is in the shadowed area in the lower portion of the stomach and is not shown clearly in this photograph.**

granulocytes. The outer layer of the sac was composed of fibrous connective tissue in which there were many small blood vessels. Sections from the wall of the aneurysm at its opening into the stomach showed tuberculous granulation tissue involving all of the layers of the stomach wall. No acid-fast bacilli were demonstrated in sections of the aneurysmal sac. Miliary tubercles, some with caseous centers and Langhans' giant cells, were found in the lymph nodes near the aneurysm, in the liver, and in the spleen. The large caseous node in the mediastinum showed active tuberculous inflammation. Sections from the scars in the apices of the lungs showed fibrosis but no tuberculous tissue. No other significant lesions were found.

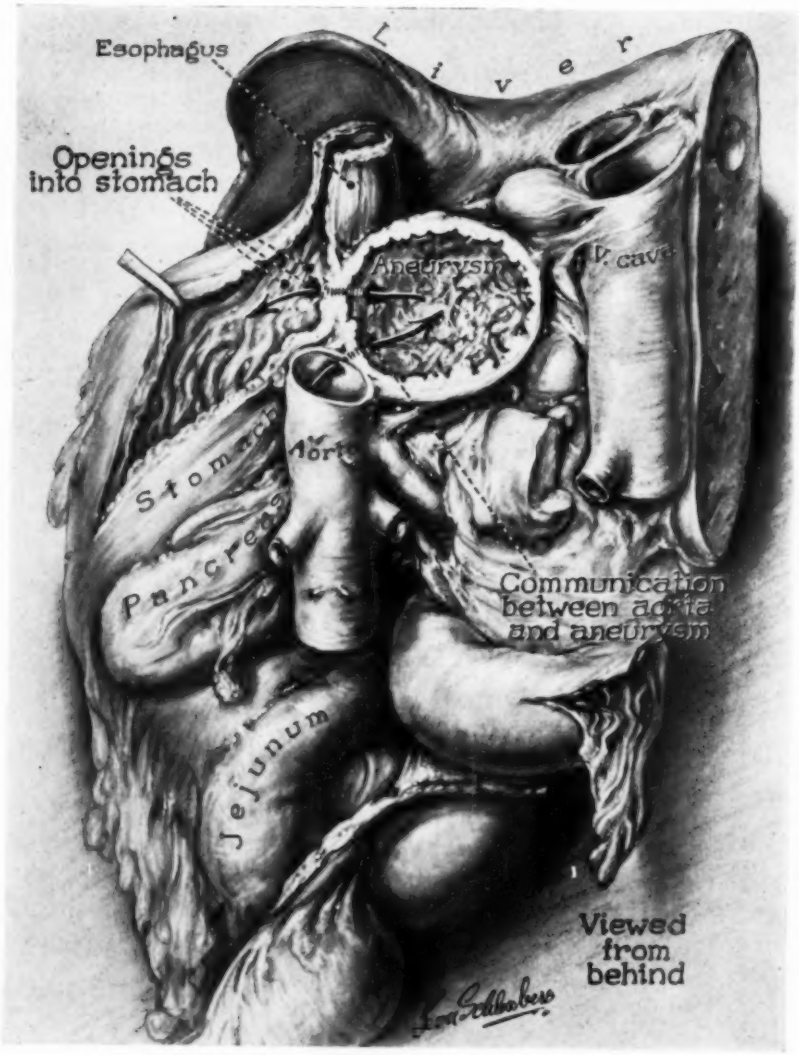


Fig. 4.—A drawing of the stomach, central portion of the liver, a segment of the aorta, and the aneurysmal sac, removed en bloc and viewed from the posterior aspect.

## DISCUSSION

Although the apical scars showed fibrosis only and no tuberculous inflammation was demonstrated on microscopic examination, it may be assumed that the bilateral, scarred areas in the lung apices were healed tuberculous lesions; that the caseous tracheobronchial node resulted from tuberculous pulmonary lesions; that tissue, presumably a lymph node, lying between the aorta and the stomach was then involved with tuberculosis (though the course of this invasion is not explained); that the tuberculous process in this area extended into the walls of the aorta and of the stomach; that when the muscular coat of the aorta was

destroyed, there was massive hemorrhage expanding this tissue into a false aneurysmal sac; and that rupture then occurred through the weakest point, which was the adherent stomach wall. It is interesting to speculate on the role of the two smaller openings of the aneurysmal sac into the stomach and whether the hematemeses eight weeks and five weeks, respectively, before death were from these. There were three episodes of hemorrhage and three openings, all of which were plugged with fibrin at the time of death.

The miliary tubercles in the neighboring nodes, in the liver, and in the spleen are thought to have come from hematogenous spread from the tuberculous infiltration of the aortic wall, the latter the result of extension of the process from the adjacent tuberculous tissue and not itself hematogenous. The only two instances of the last named type of incidence that we have been able to find are the cases of Owens and Bass[1] and of Brooks and Dawson,[2] which have been cited.

## SUMMARY

1. The twenty-three reported cases of tuberculous aneurysm of the abdominal aorta have been reviewed briefly.

2. The forty-one reported instances of rupture of an aneurysm of the abdominal aorta into the gastrointestinal tract, five of these into the stomach, have also been reviewed and three cases from the literature have been added.

3. These have been tabulated serially with those of Rottino[4] and of Hunt and Weller.[5]

4. A case of tuberculous aneurysm of the abdominal aorta which ruptured into the stomach has been reported. An aneurysm of this type with rupture at this site seems to be unique in medical literature.

Since this report was accepted, there has come to the attention of the authors the article of Dr. R. B. Pomerantz (AM. HEART J. 37:142, 1949) in which he referred to two additional cases of rupture into the jejunum (one of his own), and one case of rupture into the stomach.

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# Abstracts and Reviews

## Selected Abstracts

**Ramos, J. G., Mendez, R., and Rosenblueth, A.: Studies of Flutter and Fibrillation. VI. Effects of Acetylcholine and Epinephrine on the Ventricular Muscle of Mammalians.** Arch. Inst. Cardiol. de Mexico **18**:301, 1948.

The effects of acetylcholine and epinephrine on the ventricle of cats were studied under Dial anesthesia after exposure and denervation of the heart and ligation of the adrenal glands. The results thus obtained were confirmed on heart-lung preparations in dogs.

Ventricular fibrillation was induced by acetylcholine, small doses of epinephrine, potassium chloride, and by block of some of the capillaries following the injection of talcum powder or air.

Fibrillation rarely stopped spontaneously, but it could be interrupted by injection of large doses of epinephrine (0.1 to 0.3 mg.) and by massage. Fibrillation always ended simultaneously in all points of the ventricle. The most frequent mode of termination was transformation of fibrillation into flutter, which was followed by reversion to normal rhythm.

The discussion emphasizes the significant difference existing between ventricular, auricular, and nodal tissues in regard to the action of acetylcholine. The action of the latter does not require nerve endings and is effected without other chemical mediation.

The theory that fibrillatory activity presents continuous random waves is supported by the present study.

LUISADA.

**Massias, C.: Ortner's Syndrome in the Course of Mitral Stenosis.** Arch. d. mal. du coeur **41**:261, 1948.

The author reports a case of mitral stenosis and discusses the causes and frequency of this uncommon syndrome. Although Ortner believed that paralysis of the left recurrent laryngeal nerve resulted from compression of the dilated left auricle, subsequent workers have stated that it was the result of either compression by the dilated pulmonary artery or neuritis.

Since in this reported case, the paralysis disappeared after digitalization, the author believed that the explanation of Ortner was the correct one for his case.

LUISADA.

**Cappa, A., and Sanero, F.: Intravenous Recorcaine in Therapy.** Clin. Nuova (Rome) **6**:29, 1948.

The studies of Leriche demonstrated the sympatholytic action of procaine when injected intra-arterially. Since this demonstration, the drug has been applied in a number of conditions.

The author has used a preparation of procaine (Recorcaine) in bronchial asthma, Ménière's syndrome, anuria of glomerulonephritis, urticaria, and thromboangiitis obliterans. The dose used by the author was 1.0 Gm. of procaine dissolved in 1,000 c.c. of physiologic salt solution and injected by the drip method over a period of from sixty to eighty minutes.

The results have been extremely favorable. No disturbance followed the treatment.

LUISADA.

**Allen, W. J.: The Action of Adrenaline, Ephedrine and Methedrine on the Circulation in Man.** Clin. Sc. 6:269 (Jan.), 1948.

The effects of intramuscular injections of adrenaline, ephedrine, and Methedrine on the rate of blood flow in the human forearm and hand have been investigated by the use of the venous occlusion plethysmograph.

Adrenaline, when given intramuscularly in doses of 1.0 mg., acted rapidly, effects being conspicuous within one and one-half to two minutes, and maximum five minutes after completion of the injection. Strong palpitation, tremor, epigastric discomfort, apprehension, and sometimes headache or fullness of the head were invariably produced by this dose of adrenaline. Pallor was marked. After subcutaneous injection, the effects began later and were less intense. Following intramuscular injection the severe subjective symptoms usually lasted no longer than ten minutes, after which they became relatively mild, whereas the circulatory effects persisted for a considerable time. Tremor was the most persistent manifestation. The heart rate was only slightly and variably affected, averaging an increase of 10 beats per minute. Blood flow in the forearm also showed wide variation from case to case, but an increase was always produced. In seven cases the flow rose to an average of two and one-half times its resting value. One hour after the injection the blood pressure had begun to fall, the heart rate and forearm flow were still elevated, and palpitation and tremor persisted.

Ordinary intramuscular doses of adrenaline raise the systolic blood pressure, lower the diastolic or leave it unchanged, accelerate the heart to a small degree, and cause a considerable increase in the blood flow in the forearm.

In a similar series of experiments intramuscular injections of 60 mg. and 90 mg. of ephedrine hydrochloride were used. The action of the substance began later than that of adrenaline, and the full effect was not attained until thirty minutes after administration. Some palpitation was always produced. The action of the drug extended over several hours. Changes in heart rate were small and irregular, the composite analysis showing that the larger dose produced a protracted decrease of about 10 beats a minute. As in the case of adrenaline, the forearm blood flow varied irregularly but was always increased, though to a smaller extent than when adrenaline was used

Thus, intramuscular doses of 60 mg. and 90 mg. ephedrine hydrochloride differ in effect from those of 1.0 mg. adrenaline in that the systolic pressure is usually more greatly increased, the diastolic pressure is either raised or unchanged, and is scarcely ever lowered, the heart tends to be slowed rather than quickened, and the forearm blood flow is increased to a smaller extent than when adrenaline is used.

The dose of Methedrine used was 20 mg. in each case. The heart rate varied in an unpredictable manner but tended to show a certain parallelism with the blood flow in the forearm which was increased in all cases to a very variable degree, both from one subject to another and in each subject during the course of each experiment.

An intramuscular injection of 0.5 mg. adrenaline, after intravenous atropine, had a temporarily greater pressor effect than 1.0 mg. adrenaline alone, and the heart rate remained at the high level of 125 per minute induced by atropine. Adrenaline alone increased the blood flow in the forearm from 2.0 to 6.0 c.c. per minute. Atropine increased the flow from 2.0 to 4.0 c.c. and an additional injection of 0.5 mg. adrenaline further raised the flow to nearly 10 c.c. per minute.

Injection of 90 mg. ephedrine hydrochloride produced a rather greater rise of arterial pressure, particularly diastolic, when preceded by atropine than when given alone. Whereas ephedrine used alone slowed the heart, it quickened the rate greatly after atropine. As in the case of adrenaline, the forearm blood flow was increased over and above the small rise which followed the intramuscular injection of atropine.

When Methedrine was tested, subjects were chosen who had shown a protracted slowing of the heart after a 20 mg. dose. Atropine affected the response to Methedrine in the same way that it did the response to ephedrine. The pressor effects, both systolic and diastolic, were increased, the heart rate rose rather than fell, and the forearm blood flow increased.

In man, adrenaline, ephedrine, and Methedrine, acting directly on the heart, all tend to accelerate the rate, but in most individuals the vagus tone is sufficient to permit only a small increase in rate or to produce an actual slowing. Atropine in 2.0 mg. doses effectively removes this restraint.

The response of blood flow to intramuscular adrenaline after sympathectomy was essentially the same as in the normal forearm. This was also the case with ephedrine. This suggests the action is largely peripheral. All of these substances seem to be able to bring about an active dilatation of the blood vessels in skeletal muscle, but, as with the action on the skin, adrenaline is the most effective.

Doses of adrenaline and ephedrine increase the cardiac output and apparently decrease the total peripheral resistance, adrenaline producing the larger effect in both instances. The results here described suggest that skeletal muscle is probably the main site of this decreased resistance. The greater dilatation observed with adrenaline than with ephedrine agrees with the greater decrease in total peripheral resistance after adrenaline and is probably a factor in the lowering of diastolic pressure by adrenaline, while ephedrine raises it. In general, the results show a very ready dilatation of muscle vessels by adrenaline, a much smaller dilatation by Methedrine, and an intermediate action by ephedrine.

These substances in those doses, which strongly dilate muscle vessels, lead to a considerable lowering of peripheral resistance and allow some acceleration of the heart, while no acceleration, or actual slowing, is found when the muscle dilatation is small. In general, the diastolic blood pressure is normal or low when muscle flow is high, and vice versa.

BELLET.

**Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: Low Blood Pressure in Diabetic Coma.** Clin. Sci. 6:247 (No. 4), 1948.

It has long been recognized that in the later phases of diabetic coma the blood pressure may fall to low levels, and that this change is often irreversible, death following within a few hours. Efforts to raise the arterial pressure by drugs have been on the whole unsuccessful, while large intravenous infusions, given in the belief that the falling blood pressure was due to a diminished blood volume and a decreasing cardiac output, have frequently resulted in pulmonary edema.

The low blood pressure in diabetic coma is due to a decreased total peripheral resistance, which is below 50 per cent of the normal value. The site of the vasodilatation has not been determined. The cool, pale skin suggests that skin blood flow is diminished. Attempts to combat the peripheral vasodilatation by constrictor drugs have so far failed. The vasoconstrictor drugs, pitressin, digitalis, and d-N-methyl amphetamine hydrochloride (Methedrine), fail to raise the low arterial pressure, or show only a small transient effect. The vessels may show a transient initial constriction, but then appear to become insensitive to further injection of the drugs.

BELLET.

**Cohen, S. M., Edholm, O. G., Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: Cardiac Output and Peripheral Blood Flow in Arteriovenous Aneurysm.** Clin. Sci. 7:35 (No. 1), 1948.

The observations were made on twelve patients. All were men and all had been wounded less than two years previously except two, Case 10, who had been wounded five year years before, and Case 12, whose aneurysm had been present for twenty-nine years.

Cardiac output and right auricular pressure were studied by the technique of cardiac catheterization. Blood flow was measured in the forearm and in the leg by means of a venous occlusion plethysmograph. The arm was immersed in a water bath at 34° C., while the leg was in air at room temperature. Circulation through the aneurysm was shut off by digital pressure proximal to the aneurysm. In order to allow time for the circulation to reach a steady state, closure was maintained for one minute before the right auricular samples were withdrawn. Blood flow changes in the limbs were recorded within thirty seconds of closure of the shunt.

Cardiac output in liters per minute per 100 c.c. oxygen consumed was increased above the normal average of 2.2 in nearly all cases, the highest figure being 4.5 in a patient with a very large aneurysm. The venous filling pressure and heart rate were moderately increased. The increased cardiac output in large arteriovenous aneurysms has some relationship to the size of the communication. Closing the arteriovenous fistula by compressing the artery proximal to the shunt pro-

duced slowing of the heart rate, increase in the diastolic blood pressure, a considerable decrease in cardiac output, and a small decrease in right auricular pressure. In large shunts neither cardiac output nor right auricular pressure fell to normal levels on closure.

Two milligrams of atropine, intravenously, increased cardiac output to high levels, but changes in rate, cardiac putput, and auricular pressure were still produced by temporary closure of the shunt. Output changes on closure are more related to heart rate than to filling pressure changes.

The blood flow in limbs unaffected by the shunt was within normal limits and showed a conspicuous increase on closure of the shunt. This increase was greatly reduced by procaine block of the mixed nerves to the limb, suggesting that the increased flow was mainly due to vasodilatation and only in part produced by the rise in mean blood pressure. Blood flow in the affected limb distal to the arteriovenous fistula was reduced in lesions which had been present up to two years, was normal in lesions present up to five years, and conspicuously was increased in a lesion of twenty-nine years' duration. The flows recorded after compression of the artery proximal to the fistula suggested that in early lesions most of the blood entering the distal part of the limb traverses the aneurysm, while in long-standing lesions much arrives through other arterial channels. Resting blood flow in a limb one month after quadruple ligature was the same as in the normal contralateral limb and the vascular responses to raising body temperature were identical.

BELLET.

**Lewis, J. H., and Ferguson J. H.: Thrombin Formation. I. The Role of Calcium, Serum AC-Globulin and Tissue Thromboplastin.** J. Clin. Investigation **6**:778, 1948.

These investigators studied the clotting time in vitro of blood to which had been added in varying amounts prothrombin, serum accelerator-globulin (ac-globulin), tissue thromboplastin, thrombin, and fibrinogen. They concluded that the four substances, prothrombin, serum accelerator-globulin, thromboplastin, and calcium, are necessary for thrombin formation and that the yield of thrombin depends on the proportions of these substances. It was shown first that a thrombin yield is directly dependent on calcium concentration; second, that accelerator-globulin increased both the rate of formation and the yield of thrombin from a given amount of prothrombin, thromboplastin, and calcium, and, therefore that accelerator-globulin was necessary for the formation of any thrombin. Thromboplastin exerted effects similar to calcium and accelerator-globulin; without tissue thromboplastin no thrombin was formed. It is concluded that thrombin yield, as well as a rate of formation, is dependent on the quantity of each of these four reagents.

WAIFE.

**Carrillo, E. G.: Comments on Two Rare Diseases in Costa Rica.** Rev. argent. de cardiol. **15**:112, 1948.

The authors state that both myocardial infarction and subacute bacterial endocarditis are rare in Costa Rica. Out of 8,000 autopsies, myocardial infarction was found in only 0.2 per cent and subacute bacterial endocarditis in only 2.7 per cent.

The rare occurrence of infarction is explained by the low-fat, low-calorie diet of the poor population, in conjunction with the mild climate. The rare occurrence of the bacterial endocarditis is attributed to an immunity established at a young age on account of extremely common local focal infections.

LUISADA.

**Webster, B., and Reader, G. G.: The Effect of Antisyphilitic Treatment on the Microscopic Appearance of Syphilitic Aortitis.** Am. J. Syph., Gonor., & Ven. Dis. **32**:19 (Jan.), 1948.

Microscopic sections of the aortas of forty-five patients with gross evidence of syphilitic aortitis at post-mortem examination in whom clinical data were available were studied to determine the effect of treatment on the microscopic picture of syphilitic aortitis. The patients were

divided into three groups according to whether they had received "adequate" treatment, "inadequate" treatment, or no treatment.

Nineteen patients had been adequately treated with approximately twenty or more arsenical and twenty or more bismuth injections. Another nineteen patients had received no treatment or such a negligible amount that it could not conceivably have affected the course of their disease. All of the untreated patients showed an active syphilitic process. Only three of the adequately treated patients, on the other hand, showed active inflammation, although one other patient, whose aorta showed minimal cellular reaction, exhibited some endarteritis. Of the patients who had received inadequate treatment, five of the seven showed activity of the syphilitic inflammatory process. Eighteen patients among the forty-five investigated (or 40 per cent) gave a history of primary or secondary syphilis or had been diagnosed as latent syphilis a known number of years before death. No correlation was demonstrable between duration of infection and activity of aortitis. In ten of nineteen of the untreated patients and seven of nineteen of the adequately treated patients, syphilitic aortitis, valvulitis, or aneurysm was the cause of death. Only three patients in this series received penicillin as part of their therapy. Two of these showed an inactive aortitis while the third received penicillin such a short time before death that alteration of the pathologic picture could not be expected.

In conclusion, the authors found that only three of nineteen patients who had received adequate treatment showed an active type of syphilitic aortitis, while all of nineteen untreated patients showed active cellular infiltration of the aorta.

BELLET.

**Stryker, W. A.: Traumatic Saccular Aneurysm of the Thoracic Aorta.** Am. J. Clin. Path. **18:**152 (Feb.), 1948.

The author describes a saccular aneurysm of the thoracic aorta in an 18-year-old girl which followed an automobile accident in which there was injury to the chest. Death occurred six months later. Necropsy revealed subacute bacterial endaortitis in the aneurysm and, in addition, organizing fibrinous pericarditis, chronic purulent interstitial myocarditis, and verrucous mitral and aortic valvulitis. Incomplete tears of the aorta following trauma are described in two other patients.

KLINE.

**Rosenbaum, H., and Linn, H. J.: Tuberculoma of the Myocardium in a Patient With Tuberculous Meningitis Treated With Streptomycin.** Am. J. Clin. Path. **18:**162 (Feb.), 1948.

The case reported is that of a 21-year-old white man with pulmonary tuberculosis complicated by tuberculous meningitis. He was given 171 Gm. of streptomycin intramuscularly and intrathecally over a period of two and one-half months without beneficial effect. No significant cardiac alterations were noted except a sinus tachycardia and a gradual fall in blood pressure during the last days of life. At post-mortem examination the heart weighed 180 grams. A tuberculoma was present in the interauricular septum which projected into the right auricle.

The incidence, etiology, and pathogenesis of the lesion are briefly discussed.

KLINE.

**Garrey, W. E., and Townsend, S. E.: Neural Response and Reactions of the Heart of a Human Embryo.** Am. J. Physiol. **152:**219 (Feb.), 1948.

The sinus, atrium, and two ventricular portions of the heart of a human embryo of approximately 13 weeks of fertilization age were examined for the effect of temperature and vagal stimulation on automaticity and contractility. The heart of this 100 mm. embryo was rapidly chilled in Ringer's solution (5°C.) and then gradually warmed for the experimental periods. The heart could be kept beating for hours.

Acetylcholine bromide in concentration up to 1:10,000 had no inhibiting effects on the ventricles and only a slight and delayed inhibitory effect of the sinus-atrium preparation. The sinus

preparation beat at all temperatures between 10° and 40°, with an intrinsic rate of 157 at 37° centigrade. This rate approximates that of adult mammalian hearts when free of nervous regulation. It is assumed that the inhibitory function of cardiac nerves is a late fetal development.

HECHT.

**Kremer, W. F.: Blood Pressure Changes in Response to Electrical and Chemical (Acetylbetamethylcholine) Stimulation of the Cerebral Cortex in Dogs.** Am. J. Physiol. **152**:314 (Feb.), 1948.

In eleven dogs under sodium amytal or Dial anesthesia, electrical or chemical stimulation of certain areas of the brain evoked a fall in systolic and diastolic blood pressures. Two particularly responsive areas were found that evoked a profound fall in pressure when brought in contact with a small amount of 2.5 per cent solution of acetyl-beta-methylcholine. These two areas were the posterior sigmoid gyrus near the midline and the anterior ectosylvian gyrus. This action was conspicuously prolonged when these regions were pretreated with prostigmine salicylate powder. Local application of acetyl-beta-methylcholine appeared superior in action, lasted longer, and was confined to more circumscribed regions than the usual faradic stimulation.

HECHT.

**Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., and Banfield, W. G., Jr.: Coronary Sinus Catheterization for Studying Coronary Blood Flow and Myocardial Metabolism.** Am. J. Physiol. **152**:340 (Feb.), 1948.

A slightly modified Cournand catheter was inserted through the external jugular vein into the auricles of forty-five dogs. The catheter was allowed to slip into the inferior vena cava and then was gently withdrawn. The tip was turned and shifted slightly anteromedially. In this position the tip of the catheter pointed directly toward the coronary sinus ostium and when thrust forward, entered the sinus by rounding a sharp initial bend. The position of the sinus and the contributory veins was clearly visualized by retrograde injection of Diodrast. All manipulations were performed on the anesthetized animal under fluoroscopic control and in the right anterior oblique position.

Coronary venous blood revealed extremely low oxygen saturation with an average of 4.1 volumes per cent (22 per cent saturation). Extremely high coronary arteriovenous differences were likewise found for blood lactate and pyruvate, indicating a high rate of myocardial utilization. Glucose was removed by the heart in relatively small amounts.

Autopsy studies revealed a high incidence of endocardial damage; only three of 28 dogs were found to be free of evidence of catheter injury. These consisted of small subendocardial hemorrhages and mural thrombi. The lesions occurred along the insertion of the catheter including the tricuspid and the pulmonary valves. If the catheter was inserted deep into the coronary sinus, lesions secondary to obstruction of venous outflow occurred, with gross myocardial hemorrhages in regions drained by the great cardiac veins. Standard lead electrocardiograms revealed alterations of RS-T segment and of the T wave suggesting subepicardial injury which could be demonstrated in two examples at autopsy. The injuries peculiar to deep coronary sinus catheterization may be avoided if the catheter is inserted not more than two cm. into the coronary sinus. Bursts of extrasystoles were frequently noted when the catheter touched ventricular muscle just beyond the tricuspid valve or the regions below the pulmonary conus. Cardiac catheterization may be considered a safe procedure only if definite precautions are observed.

HECHT.

**Eckenhoff, J. E., Hafkenschiel, J. H., Harmel, M. H., Goodale, W. T., Lubin, M., Bing, R. J., and Kety, S. S.: Measurement of Coronary Blood Flow by the Nitrous Oxide Method.** Am. J. Physiol. **152**:356 (Feb.), 1948.

Simultaneous determination of coronary blood flow by the use of a bubble flowmeter and by direct sampling of blood from the coronary sinus either by direct canalization or by sampling through a cardiac catheter was performed in dogs with nitrous oxide as the tracer agent. Blood flow was calculated as flow per 100 grams of myocardium drained on the basis of nitrous oxide

concentration in coronary venous blood and in arterial blood over a ten-minute period of gas inhalation. Values of 63.7 ml. per 100 grams of tissue were obtained by the bubble flowmeter technique, 67.8 ml. per 100 grams by direct canalization. Blood samples obtained by venous catheterization revealed values of 71.3 ml. per 100 grams of tissue. The slightly higher values by the indirect method may be the result of contamination by noncoronary venous blood.

HECHT.

**Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A.: Studies of the Pulmonary Circulation at Rest and During Exercise in Normal Individuals and in Patients With Chronic Pulmonary Disease.** Am. J. Physiol. **152**:372 (Feb.), 1948.

Measurements of cardiac output and pulmonary arterial pressures were recorded by the catheter method during rest and exercise in three normal subjects and in eight patients with a variety of pulmonary diseases. In the normal group mean pressure in the pulmonary artery and vascular resistance in the lungs fell and the work of the right ventricle rose insignificantly. In patients with chronic pulmonary disease the expansibility of the pulmonary bed during exercise was limited, as demonstrated by a significant rise in pulmonary artery pressures on exercise. The work of the right ventricle was invariably higher than in normal subjects on a corresponding work level.

HECHT.

**Wolff, L., and Sagall, E. S.: Intravenous Administration of Mercurial Diuretics in Man; Immediate Effect on the Electrocardiogram.** Arch. Int. Med. **81**:137 (Feb.), 1948.

Three hundred nineteen intravenous injections of three different mercurial diuretic preparations were administered to 137 patients. Of these, 121 were suffering from chronic congestive heart failure, seven from cirrhosis of the liver, six from the nephrotic stage of chronic glomerulonephritis, and three from thyrotoxicosis. An initial four-lead electrocardiogram was taken on each of the patients, but during the study only Lead II was employed. The electrocardiographic pattern was recorded continuously during the period of the administration of the drug and at one-, two-, three-, and four-minute intervals after completion of the injections.

Significant electrocardiographic abnormalities were seen after thirty-six (11 per cent) of the 319 injections. Of the 137 patients investigated twenty-seven (20 per cent) showed significant changes in the electrocardiogram. The type of disease present seemed to play no role in the incidence of abnormalities, nor did the type of mercurial used. The results did not differ in the two sexes. The abnormalities found were auricular premature beats seven times and ventricular premature beats twenty-six times. In two cases, both auricular and ventricular, ectopic beats were found. In five cases the ventricular premature beats arose from different foci. Paroxysmal ventricular tachycardia occurred on one occasion.

This study shows that there is a preponderance of ventricular abnormalities suggesting that the ventricle is more susceptible to the action of mercury than is the auricle. Further, the cardiac mechanism prior to injection does not affect the incidence of electrocardiographic abnormalities induced by the drug, with the possible exception of auricular premature beats. Untoward reactions occur even though previous injections were uneventful, and vice versa. Digitalis does not predispose to the production of arrhythmias after the intravenous injection of mercurial diuretics.

BERNSTEIN.

**Liljestrand, G.: Regulation of Pulmonary Arterial Blood Pressure.** Arch. Int. Med. **81**:162 (Feb.), 1948.

The author used anesthetized cats in which a special cannula was inserted in the pulmonary artery in such a way that the wall was gripped between two flanges and connected with a vertical glass tube and piston recorder. The thorax was closed so that spontaneous respiration was established in most cases.

Epinephrine in doses of 0.005 to 0.02 mg. and ergotamine, 0.3 mg., had a direct effect on the vessels of the pulmonary tree. Nervous mechanisms could not be demonstrated to affect pulmonary arterial pressure. Carbon dioxide produced small increases in pressure which remained after vagotomy, but could be abolished or reversed by ergotamine. Oxygen want produced a rise in pulmonary arterial pressure, whereas oxygen inhalation resulted in a drop. These effects were produced by variations in the degree of contraction of the arterioles and precapillaries of the lungs. The effect is not abolished by vagotomy or extirpation of the stellate ganglions or by the administration of ergotamine, dihydroergotamine, atropine, or yohimbine. The author feels that since it is a local effect, it is possibly based upon the degree of oxygenation of the venous blood in the arterioles of the lungs.

Though increase of carbon dioxide and decrease of oxygen both act to raise the arterial pressure, the effect of oxygen want is much stronger. The author concludes, therefore, that oxygen want which leads to vasodilatation in the systemic circulation acts in the opposite way in the pulmonary circulation, thereby directing blood away from badly ventilated parts of the lung to those parts which have better oxygenation. He further feels that the decrease in vital capacity after the inhalation of oxygen is produced at least in part by the dilatation of the vessels of the lung. He also believes that since anoxia increases the arterial and precapillary pressure in the lungs, the slowing of the circulation may lead to oxygen want without causing back pressure and may therefore be an important factor in the production of edema.

The author attempts to explain some of the toxic effects of oxygen on the basis of these experiments and states that the hyperemia caused by the inhalation of 100 per cent oxygen at a pressure of one atmosphere is simply the result of the physiologic dilating effect of oxygen on the arterioles and precapillaries. The edema which results is caused by the inability of the lymph vessels of the lung to carry off fluid from the lungs because of their compression by the widened arterioles and precapillaries. The disturbance of the balance between formation and removal of the lymph will result in edema.

BERNSTEIN.

**Glomset, D. J., and Birge, R. F.: Morphologic Study of the Cardiac Conduction System; the Pathogenesis of Heart Block and Bundle Branch Block.** Arch. Path., 45:135 (Feb.), 1948.

The authors review the history of the development of the current conceptions of heart block and bundle branch block, recalling the result of previous investigators who have known that bundle branch block can result from injury to the interventricular septum. They believe, however, that the cause of this disturbance is in the septal myocardium and not in the bundle of His or its main subdivisions.

The authors are guided by Glomset's previous studies, reiterated in the present report, showing that the bundle of His does not exist in the human being; that what has been described as the bundle of His is nothing more than a small fasciculus of ordinary cardiac muscle devoid of significance, which extends up from the ventricular septum into the auriculoventricular ring.

They conclude that heart block and bundle branch block have no basis in the pathologic disturbances of a conduction system, inasmuch as the latter hardly exists in the human heart. They believe that these lesions, heart block and bundle branch block, develop on the basis of damage to the upper part of the ventricular septum. They also conclude that Purkinje fibers, while they exist in human hearts, have in reality little or no differentiating structural development, their apparent characteristic morphology being due to post-mortem degeneration; that their reputed glycogen content is nonexistent, and their swollen appearance, a mechanical artefact.

The authors analyze the pathologic data in fifty-eight cases of heart block and bundle branch block drawn from the literature, and twenty-one cases personally studied. They believe that replacement fibrosis secondary to arteriosclerosis in the upper part of the ventricular septum is the important cause of what has hitherto been considered conduction system pathology. It is difficult to find a preponderance of this damage on one or the other side of the septum; rather, in their opinion, it is diffuse in the majority of cases. Therefore, they believe that in bundle

branch block the electrocardiographic pattern is determined by the pre-existing preponderance brought about by the underlying etiological factors.

The authors emphasize that in A-V heart block, in "90 per cent of the recorded cases, a considerable portion of the septal myocardium had been destroyed"; likewise, a high percentage of the various types of bundle branch block showed a similar lesion. When an infarct occurred in the upper part of the septum, the right coronary artery was almost always the site of occlusion. Conversely, 10 per cent of the cases of heart block and 20 to 30 per cent of the cases of bundle branch block did not show any morbid changes in the ventricular septum. It is pointed out that in such cases the rich intrinsic nervous system comprising numerous ganglia in the atria may be at fault and responsible either in a primary or in an accessory manner for heart block and bundle branch block.

GOULEY.

**Will, O. A., Jr., Rehfeldt, F. C., and Neumann, M. A.: A Fatality in Electroshock Therapy.** J. Nerv. & Ment. Dis. **107**:105 (Feb.), 1948.

The authors review thirty-three fatalities following electroshock therapy which they have collected from the literature and record one case of their own.

The initial treatment in the authors' case was uneventful and two days later a second was given, with 6 c.c. of curare being given intravenously. A grand mal attack occurred. About five minutes after the cessation of the convulsion, generalized muscular twitchings were noted and the patient suddenly ceased breathing. The patient showed no spontaneous response to the artificial respiration. The heart beat was audible for at least fifteen minutes after the cessation of respiration.

Clinically the death seemed to be the result of respiratory failure and it was thought that the cause might have been damage to medullary centers by the electric current or by changes in the blood and intracranial pressures.

At necropsy the brain was swollen, the convolutions were flattened, and the meningeal coverings were dry. Only 25 c.c. of intracranial fluid was collected during the removal of the brain. Arteries at the base of the brain were unusually narrow and thin walled and free from arteriosclerosis. The circulatory system gave no evidence of a disease process. The aorta was hypoplastic. The cause of death was given as acute cerebral edema and medullary compression.

BELLET.

**Sirry, A.: Radiological Study of Bilharzial Cor Pulmonale.** J. Roy. Egyptian M. A. **31**:146 (Feb.), 1948.

The object of this communication is to report the radiologic picture in bilharzial Ayerza's disease and its radiological differentiation from other forms of chronic cor pulmonale.

Six cases were chosen as examples of bilharzial cor pulmonale. The diagnosis in two patients was confirmed by necropsy. All patients gave a history of bilharzial infection of some years' duration, and in all, ova were found in both urine and stools. This suggests that bilharzial cor pulmonale follows a rather severe infection of bilharziasis, and is the result of long-standing arterial obstruction.

Clinically the cases presented the following features: bilharzial livers and enlarged spleens; cyanosis, in two cases, accompanied by congestive heart failure; and the clinical signs of an enlarged pulmonary artery and conus. Only one patient with a huge aneurysmal dilatation of the pulmonary artery showed a regurgitant pulmonary murmur.

The radiological study of these patients showed the following: enlargement of the pulmonary artery and conus; prominent hilar shadows; enlargement of the right ventricle and auricle; slight or no enlargement of the left side of the heart; restricted movement and elevation of the left cupola of the diaphragm; no indication in the lung fields of the lesions described as common in pulmonary bilharziasis; and normal position and size of the ascending aorta in every case. The size and position of the aorta are the most important radiologic differential signs

suggested by this study. In bilharzial cor pulmonale the ascending aorta is normal in size and position. These conditions occur in young persons in whom acquired aortic pathology is usually absent.

BELLET.

**Sollmann, T., and Estable, J. J.: The Action of Procaine, Salicylate and Benzoate of Sodium on the Excitability of Skeletal Muscle and of Nerve.** Anesthesiology **9**:188 (March), 1948.

The authors' investigations were made on preparations of the sciatic nerve and gastrocnemius muscle of frogs, immersed in a Ringer salt solution kept near 0° centigrade.

Survival of the nerve and muscle is not prolonged by brief or continued sojourn in any concentration of procaine hydrochloride. All concentrations that have any effect at all produce progressive depression of response to stimulation and shorten the survival time. The response of muscle to direct stimulation is almost quantitatively parallel to the depression of response to nerve stimulation. The speed and degree of the depression increase with the concentration of the procaine. Reversibility by transfer to unpoisoned Ringer solution seems to depend on the concentration of procaine and the time of contact more than on the degree of depression.

As a comparative test of direct muscular depression by procaine hydrochloride, sodium salicylate, and sodium benzoate, the solutions were injected into the peripheral end of the ligated femoral artery of rabbits; the response was tested by faradic stimulation applied to the saphenous nerve and to the exposed muscles. It was seen that the three agents depress the direct muscular response equally as well as the reflex response. The potency of procaine hydrochloride is materially greater than that of sodium salicylate and sodium benzoate. The "pseudohernia" of procaine involves depression of muscle as well as nerve; indeed, the direct effect on muscle is greater than on nerve. Similar effects are produced by administration of 2 per cent sodium salicylate, but were not produced by 5 per cent sodium benzoate.

Satisfactory local anesthesia was obtained with 0.2 per cent solution of procaine hydrochloride and with 2 per cent and 5 per cent solution of sodium salicylate, but only light anesthesia resulted when a 5 per cent solution of sodium benzoate was employed. Integration of the observations suggests that sodium salicylate in 2 per cent solution could be used for injection anesthesia, but that it is materially inferior to procaine, being less potent and more irritant. The anesthetic action of sodium benzoate is demonstrable but too feeble for practical use.

The experiments with excised nerve and muscle show that the paralysis resulting from procaine hydrochloride become irreversible if the relatively high concentrations act for relatively long periods.

BELLET.

**Maggioni, G. F.: Salicylate Therapy in Children.** Arch. Dis. Childhood **23**:40 (March), 1948.

Some observations are presented in this paper on the fate of salicylates in normal and rheumatic children. The efficacy and specificity of this therapy are not discussed. No restrictions were placed on food or liquid intake during these observations.

The intravenous administration of salicylate was not used, because this route of administration has no practical advantage. The drugs used orally in the routine treatment of rheumatic fever were (a) sodium salicylate (1 part) with sodium bicarbonate (2 parts) in a liquid mixture of which ½ ounce was said to contain 20 grains of the drug; (b) aspirin, five grains per tablet; and (c) calcium aspirin, 5 grains per tablet. Sodium salicylate in water, taken by mouth, was rapidly absorbed; its presence could be detected in blood and urine within fifteen to twenty-five minutes. The peak in the blood level was reached in from one and one-half to two hours. Thereafter the concentration decreased slowly. The quantity of salicylate that could be recovered from the urine of normal subjects after a single dose was about two-thirds of that ingested. In rheumatic patients treated continuously, the salicylate recovered in the urine was 50 or 60 per cent, or less, of the intake, especially during acute periods.

As there is a loss of vitamin C in acute rheumatic fever, there should be a supplementary administration of this vitamin to avoid depletion of ascorbic acid reserves. The giving of vitamin A in addition seems to be useful.

The authors conclude that an appropriate scheme of salicylate therapy in children with rheumatic fever should include the oral use of freshly prepared solutions of sodium salicylate in flavored water with sodium bicarbonate added in the proportion 1:1 when given every four hours, or 1:2 when given every two hours. The last dose in the evening and the first in the morning may be doubled to permit a longer undisturbed interval during the night. The administration by enema seems to be indicated in patients with severe vomiting. Aspirin or calcium aspirin in tablets can also be used. The quantity of sodium salicylate which in children raises the level to 25 or 35 mg. per 100 ml. is in the range of 0.12 to 0.18 grain per kilogram of body weight. The estimation of salicylate plasma level seems advisable to control the accuracy of the administration and to avoid overdosage.

BELLET.

**Cohen, M. E., White, P. D., and Johnson, R. E.: Neurocirculatory Asthenia, Anxiety Neurosis or the Effort Syndrome.** Arch. Int. Med. **81**:260 (March), 1948.

An attempt is made to summarize certain major positive findings (physical, physiological, subjective, and objective) which the authors have observed in a five-year study of neurocirculatory asthenia. The confused terminology regarding this condition is discussed and the various synonyms described. The exact limits of the terms so used are not clearly defined, but they all refer to a type of disorder in which several of the following features are striking: nervousness, easy fatigue, shortness of breath, palpitation, spells of faintness, giddiness, apprehension, poor muscular work performance, and emotional stress. However, all or any of these symptoms are not associated with any diagnosable disease of the heart, lungs, nervous system, or thyroid gland.

The authors studied 144 patients with an average age of 26.9 years. Abnormal findings were few and such positive findings that were present occurred in a high percentage of cases. These findings included a high resting pulse rate, increased respiratory rate, flushed face, hyperactive knee jerks and ankle jerks, and tremors of the fingers. In contrast to these findings was the multiple nature and high incidence of subjective symptoms. Studies of muscular work demonstrated a defect in aerobic metabolism in all grades of work. Pulmonary ventilation was abnormal as was awareness of dyspnea. The pulse rate for all grades of exercise was abnormally high. Heart size, electrocardiograms, resting circulatory measurements, and cardiac output were all normal. Quantitative studies of pain revealed an abnormal reaction to painful stimuli. All patients diagnosed as having neurocirculatory asthenia were placed in the "neurosis" category on psychological testing.

Statistics revealed a definite familial incidence with an almost "Mendelian" hereditary pattern, and the authors do not believe that environment and experiences have been demonstrated to be the major factors in causing the disorder.

From a prognostic viewpoint, a convenient distinction is made, on the basis of history alone, between acute and chronic neurocirculatory asthenia. Those diagnosed as having an acute disturbance demonstrated more nearly normal observations than did patients with chronic disease. Strong emphasis is placed on the determined fact that basal measurements made with the patients resting may not show abnormalities, while measurements made with the subject under stress may show marked differences; the stronger the stress, the greater the deviation from normal. No specific effective curative measures are proposed.

BERNSTEIN.

**Stead, E. A., Jr., Warren, J. V., and Brannon, E. S.: Effect of Lanatoside C on the Circulation of Patients With Congestive Failure.** Arch. Int. Med. **81**:282 (March), 1948.

Twenty-two patients in congestive heart failure were observed after they had received a single intravenous injection of 1.6 mg. of lanatoside C. Control observations were made on admission in all cases and repeated after the total digitalization. Cardiac output (direct Fick),

arterial pressure (femoral artery), atrial pressure, and peripheral resistance were established in all cases.

The first observed effect was an average fall in venous pressure of 62 mm. $H_2O$ which began in five to ten minutes and continued for thirty to sixty minutes. This decrease was not preceded by diuresis and appeared independent of a decrease in the blood volume. The stroke volume improved in twenty patients, but the cardiac rate was variable. There was no constant change in oxygen consumption. The mean arterial pressure usually increased with no consistent change in diastolic pressure. The peripheral resistance fell in eighteen of twenty observations. In eighteen of the twenty-two subjects, the average increase in cardiac output was 1.6 liters per minute. The increase in output resulted primarily from a decrease in arteriovenous oxygen difference and represented an increase in blood flow to the tissues of 2,300 liters per day. Also demonstrated were the facts that patients in congestive failure may have a high cardiac output which can be further increased with digitalis and that lanatoside C increases the cardiac output in the presence of a normal rhythm.

The prime action of the digitalis appears to be on the ventricular muscle which enables the ventricles to increase their output. There is a fall in atrial pressure which is primarily due to changes in venous tone. The further fall in venous pressure which may occur later appears to be related to the decrease in blood volume caused by the diuresis.

BERNSTEIN.

**Evoy, M. H., and de Takats, G.: Place of Intermittent Venous Hyperemia in the Treatment of Obliterative Vascular Disease.** Arch. Int. Med. **1**:292 (March), 1948.

After preliminary tests of the peripheral circulation, the patients were instructed to rent or buy an automatic rhythmic venous constrictor apparatus, to use it at home for two to three hours daily, and to report every three months for the first year, twice a year for the second year, and once in the third year. Improvement was measured by objective methods, the most sensitive of which were found to be venous filling time and walking ability. Subjective improvement was noted in a higher percentage than objective improvement, but subjective improvement without objective evidence of improvement was disregarded. Of 100 patients studied, sixty-seven derived some benefit, whereas thirty-three either showed no improvement or had a progression of the disease.

The authors conclude that intermittent venous hyperemia is contraindicated in acute venous thrombosis, lymphangitis, severe arteriolar obstruction, and frank gangrene. Sympathectomy is still the treatment of choice in those cases with definite spasm, but venous hyperemia appears to offer additional benefit after vasoconstrictor tone is abolished. Diabetic patients with peripheral nerve involvement, patients with pronounced vascular spasm, and those with arteriolar and capillary stasis are not suitable subjects. Patients with vascular sclerosis in whom preliminary tests show poor response to sympathectomy or those who have already undergone sympathectomy, but still have considerable claudication, constitute the group for whom this form of treatment is indicated. It is an ambulatory treatment to be used at home. "If the rhythmic constrictor did nothing else but supply the patient with a harmless placebo, it would fulfill a need in geriatric practice."

BERNSTEIN.

**Olinger, Mervin G.: Mixed Infection in Subacute Bacterial Endocarditis.** Arch. Int. Med. **81**:334 (March), 1948.

Mixed infection in two cases of subacute bacterial endocarditis which responded favorably to antibiotic therapy are reported. In one case *Corynebacterium pseudodiphthericum* and *Streptococcus viridans* were present; in the second case *Streptococcus viridans* and *Hemophilus parainfluenzae* were present. The recognition of mixed infection is important in view of the present choice of antibiotics. In one case it was obvious that both streptomycin and penicillin were essential. Adequate selection of suitable antibiotics may require identification of all the organisms involved in a given infection. It is suggested that mixed infection in subacute bacterial endocarditis may be more frequent than is reported.

BERNSTEIN.

**Findley, J. W., Jr., and Adams, W.: Primary Systemic Amyloidosis Simulating Constrictive Pericarditis.** Arch. Int. Med. **81**:342 (March), 1948.

A case of primary systemic amyloidosis is presented in which elevated venous pressure, prolonged circulation time, low pulse pressure, small cardiac movements, low electrocardiographic voltage, hepatomegaly, decreased serum albumin with a normal concentration of globulin, albuminuria, dependent edema, and ascites led to a diagnosis of contrictive pericarditis. It is not difficult to understand how the deposition of amyloid in the heart may produce a picture which simulates the syndrome produced by constrictive pericarditis. In one disease (amyloidois) there is confinement of the individual muscle fibers and in the other (constrictive pericarditis) there is confinement of the organ as a whole. One of the most interesting and unusual features of this case was the spectacular involvement of the nerves. The occurrence of steatorrhea and hypocalcemia was of interest in connection with a recent suggestion that amyloidosis may occasionally cause the sprue syndrome. Biopsy of muscle might have made the diagnosis possible in this case prior to autopsy, but in general, the authors stress the multiplicity of symptoms and the difficulty of diagnosis in the absence of a positive congo red test or certain external manifestations.

BERNSTEIN.

**Strauss, H., and Greenstein, L.: The Electroencephalogram in Cerebrovascular Disease.** Arch. Neurol. & Psychiat. **59**:395 (March), 1948.

The authors correlate clinical signs, symptoms, and duration of illness with the type of electroencephalograms in ninety-five cases of cerebrovascular accident. The great majority of patients (sixty-seven out of ninety-five, or about 70.5 per cent) with cerebrovascular disease showed no delta activity in the electroencephalogram. A positive correlation between symptoms and signs, on the one hand, and the electroencephalogram, on the other, was found to exist in only two respects: (1) in all the patients with an electroencephalographic focus, such a focus corresponded to the anatomic site of the lesion as diagnosed on the basis of the clinical facts; and (2) all the patients with clouding of consciousness showed delta activity in the electroencephalogram. All patients with a high degree of electroencephalographic abnormality of symmetric diffuse type, asymmetric diffuse type, or parasymmetric focal type showed clinically a disturbance in the state of consciousness, whereas only some of the patients with a low degree of electroencephalographic abnormality of symmetric diffuse type or a high degree of abnormality of parasymmetric diffuse type showed a similar clinical disturbance.

Normal records were seen in patients with hemispheric lesions producing hemiparesis, aphasia, hemianopsia, and combinations of such symptoms, even though the lesions were of recent origin. In other patients similar clinical findings were associated with abnormal electroencephalograms as late as one year after the onset of symptoms. These observations show that there is no correlation between the electroencephalogram and the time interval and symptoms, even though the two latter factors are considered in conjunction. However, for four of the ninety-five patients, repeat records showed a diminution in the degree of abnormality when compared with the records taken earlier in the course of the disease.

In this series of ninety-five cases of cerebrovascular disease, epileptic attacks occurred in fourteen. Of the five cases of jacksonian seizures, only one yielded a high degree of electroencephalographic abnormality of asymmetric, focal type. None of the records showed a pattern indicative of a convulsive disorder.

A comparison of the frequency of various types of electroencephalographic records in cases of cerebrovascular disease with the frequency of the same types of records in cases of hemispheric tumors demonstrates the fact that certain types of records (that is, asymmetric records and records with a focus) make the diagnosis of a brain tumor much more probable than that of a cerebrovascular lesion. It also shows that no one type of record is specific for one or the other type of cerebral lesion.

BELLET.

**Jones, N. W., and Rogers, A. L.: Chronic Infection and Atherosclerosis.** Arch. Path. 45:271 (March), 1948.

The authors report additional data to support their belief that cardiac failure, secondary to coronary atherosclerosis, will respond favorably, in certain cases, to the removal of focal infection. Their interest is centered particularly in chronic hyperplastic disease of the paranasal sinuses, in which lesion they emphasize the common occurrence of arteriolar sclerosis, of thrombosis of small arteries, and the presence in tissues of microorganisms, chiefly diplococci, presumably streptococci. The authors believe that nasal infection may reach the systemic circulation by means of the lymphatic connections between the paranasal sinuses and the paratracheal lymphatics, thence by the great veins to the right heart, a route of infection often mentioned by the otolaryngologists.

The authors are impressed by local arterial and arteriolar thickening in response to local infection. Their work does not reveal whether such changes necessarily reflect the presence of a widespread systemic atheromatosis. Their experimental work consisted of the injection of cultures of streptococci into the paralaryngeal lymph nodes of cats. The organisms were obtained from the hyperplastic antral mucosa of a patient with coronary artery disease. While such organisms were recovered on culture of the cat's aorta and coronary artery tissue, also of liver and spleen, no atheromatous coronary lesions were found in similarly treated animals allowed to live for many months.

However, the authors found some evidence for the validity of infectious lymphatic transportation from the neck to the chest. After injecting trypan blue into the paralaryngeal lymph nodes of cats, they found large phagocytes laden with the blue pigment in the walls of the ascending arch of the aorta.

GOULEY.

**Steiner, A.: Effect of Choline in the Prevention of Experimental Aortic Atherosclerosis.** Arch. Path. 45:327 (March), 1948.

The lipotropic action of choline on the fatty infiltration of the liver in depancreatized dogs led Steiner to add this substance to the cholesterol diet fed to rabbits for the production of hypercholesterolemia.

Fifty-four rabbits, divided into two approximately equal groups, one a control receiving cholesterol without the supplementary choline, were killed at periods varying from 40 to 100 days. They were autopsied with special attention being paid to the degree of aortic atheromatosis in the two contrasting groups. While the ingestion of choline did not affect the level of hypercholesterolemia, it retarded and reduced the development of atheroma in the aorta of the rabbit. Steiner found a definite quantitative relationship between the amount of choline ingested and the degree of protection against atheromatosis.

The action of choline in this respect remains unknown, differing from that of thyroid extract and of iodine, which prevent the inception of hypercholesterolemia.

GOULEY.

**Wyatt, J. P., and Goldenberg, H.: Amniotic Fluid Embolism.** Arch. Path. 45:366 (March), 1948.

The authors report a case of sudden death due to pulmonary embolism occurring in the first stage of delivery. The patient lived only fifteen minutes from the time of acute onset. Following the rupture of the membranes she became acutely dyspneic and cyanotic. Histologic examination revealed the cause, namely, amniotic fluid embolism originating most probably in the abrasion of the endometrial surface of the lower uterine segment with subsequent tearing of uterine veins and sinusoids. Microscopic examination revealed not only uterine epithelial fragments, but also mucin within pulmonary arterioles.

The diagnosis was made only by microscopic study, since this type of embolism involves small pulmonary vessels. The authors believe with Steiner and Lushbaugh, who originally reported this obstetrical catastrophe, that its incidence is undoubtedly greater than is generally known, and that it is obscured under diagnoses of acute pulmonary edema and obstetrical shock.

GOULEY.

**Leicher, F.: Pathogenesis of Primary Epithelial Tumors in Human Conduction System.** Ztschr. f. Kreislaufforsch. **37**:8 (March), 1948.

To the five instances of primary tumors of the conduction system encountered in literature two new observations are added. One concerned a woman who died at the age of 24 years after having shown A-V block for two years; the other tumor was found in the heart of a woman 34 years old who had been known to have cardiac disease since her youth. Typical Adams-Stokes seizures were present in both patients.

In the region of the A-V node in both instances there was a small tumor of an identical structure: a mixture of collagenous and connective tissue cells of varying character and cysts lined by cells of epitheloid appearance. However, atypical or polymorphic cells or mitoses were not encountered. The microscopic findings are analyzed and compared with previously described cases of tumors in the conduction system. It is concluded that these tumors are hamartomas growing from epithelial tissue, the origin of which is to be sought in elements of the caudal portion of the primitive intestine which had been displaced into the atrial septum.

BRUMLIK.

**Moll, A., and Korth, C.: Electrocardiographic Diagnosis of Left Ventricular Hypertrophy.** Ztschr. f. Kreislaufforsch. **37**:125 (March), 1948.

The well-known electrocardiographic combination of left axis deviation, depression of S-$T_1$, inverted $T_1$, and positive $T_3$ is classified as "the hypertrophy form." However, it is not simple hypertrophy and dilatation of the left ventricle which is at fault: the electrocardiographic change is due to a hypertrophied and dilated left ventricle which is also in failure because of myocardial damage.

The same pattern is found after the administration of digitalis following infarction of the anterior surface of the heart, during the course of general infections, following thyroidectomy and tonsillectomy, and when left ventricular activation is delayed. In these instances the pattern is transient; if the hypertrophy of the left ventricle, etc., is the underlying cause, the pattern is permanent.

Great emphasis is laid on a subtle distinction between the convex "hypertrophy S-T form" ("Hypertrophieform des Mittelstücks") and the sagging ("muldenförmig") depression of this segment which is considered to be a typical expression of coronary insufficiency, digitalis effect, and toxic damage of the myocardium (for example, diphtheria). In the opinion of the authors the "Hypertrophy ECG" implies a very serious prognosis.

BRUMLIK.

**Krick, J.: Transverse and Longitudinal Extensibility of Arteries.** Ztschr. f. Kreislaufforsch. **37**:140 (March), 1948.

This paper summarizes the results obtained in experiments on surviving and devitalized (desiccated or boiled) beef arteries. There is a considerable difference between the extensibility of the aorta and its branches: in the aorta the transverse extensibility is predominant, whereas the large arteries (carotid more than the femoral) rather show an increase in longitudinal extensibility. Veins possess a more pronounced transverse extensibility than arteries. After killing by desiccation and resoftening, the extensibility of the aorta and the arteries changes little; in contrast, boiling diminishes the longitudinal extensibility of the arteries considerably, but that of the aorta is diminished relatively little.

It is concluded that the extensibility of the arteries, which is a function of the histomechanical arrangement of their wall tissue, is not destroyed by dehydration but that it is diminished by heat.

BRUMLIK.

**Crosby, R. C., and Wadsworth, R. C.: Temporal Arteritis.** Arch. Int. Med. **81**:431 (April), 1948.

The essential features of forty-three previously reported cases of temporal arteritis, as well as five additional cases reported in this paper, are presented and analyzed. The pathologic

changes in biopsy specimens of artery segments in one case are described in detail and consist of a granulomatous type of reaction involving all coats of the artery but usually greatest in the media. Areas of necrosis are accompanied by a diffuse infiltration of cells in which the mononuclear varieties seem to predominate. Multinuclear giant cells are conspicuous but there is little to suggest any relationship to tuberculous, syphilitic, or rheumatic arteritis. The internal elastic lamina seems to act as an imperfect buffer against internal progression of the process to the intima; but with progression of the inflammatory process into the intima there may be destruction of the endothelial lining and the development of thrombi with obliteration of the lumen. This process can also extend through the periadvential tissue where it will surround but not penetrate the periarterial nerves. Compressions of these nerves may contribute to the pain of which these patients complain. A dissecting aneurysm of one temporal artery and phlebitis of the accompanying veins was also found. Blindness is a common complication occurring in one or both eyes of 33.3 per cent of the cases and the possible prophylactic value of section of the middle temporal artery early in the disease is suggested.

The authors conclude that temporal arteritis is a distinct clinical entity, affecting people of the older age group, which has a mortality (12.5 per cent) which is considerably less than that of most other forms of arteritis and for which the cause is unknown. The systemic symptoms probably indicate a more generalized arteritis, but since the temporal vessel involvement and symptomatology arising from it are constant and dominant features of the disease, it is suggested that the term "temporal arteritis" be retained until etiological classification is possible.

BERNSTEIN.

**Zelman, S., and Gilbert, T.: Cytochrome C Therapy of Tissue Anoxia in a Case of Hepatolenticular Degeneration.** Arch. Int. Med. **81**:485 (April), 1948.

A case of hepatolenticular degeneration (Wilson's disease) is described in which the bright venous blood and the presence of clubbing of the fingers seemed to point toward the existence of a relative anoxia. The authors, therefore, after a very complete chemical-clinical work-up prepared cytochrome C from equine hearts and administered it to their patient along with sodium succinate (shown to participate in another pathway of oxidative metabolism leading up to the cytochrome series and a known potentiator when used with cytochrome C).

The patient, a 30-year-old white veteran, seemed to require unusually large amounts of cytochrome C since the desired end point of a pink color in the plasma was obtained only intermittently with 80 mg. or more daily, intramuscularly. This pink color was believed to represent a spill-over into the serum of any unneeded excess but has been shown to be really due to the presence of hemoglobin as a result of slight hemolysis. The patient seemed to improve clinically within a few days, but the authors caution against undue enthusiasm since the intensity of symptoms of parkinsonism is commonly observed to vary with the patient's mood and remissions have been described in Wilson's disease.

After two months of continuous therapy he was able to speak, feed himself, and walk unassisted. Edema of the legs disappeared (first time in three years) and clubbing diminished. The metabolic rate returned to normal, indicating an increased consumption of oxygen. Venous blood, formerly red to purplish, now varied from blue to a deep blue-black. Arteriovenous oxygen differences, formerly below normal, were considerably increased. These facts alone indicate a definite increased utilization of oxygen by the tissues. Fatal relapse occurred when administration of cytochrome C was discontinued because of the development of eosinophilia; terminal reinstitution of cytochrome therapy proved ineffective. Autopsy revealed pathologic changes referable to anoxia, but less marked than expected. This, as well as a remarkable degree of hepatic regeneration, may have been influenced by the therapy with cytochrome C.

BERNSTEIN.

**Master, A. M.: Apical Systolic Murmur.** Arch. Int. Med. **81**:518 (April), 1948.

The author believes, and quotes numerous extensive personal and insurance statistics to support his belief, that loud apical systolic murmurs, even in the absence of cardiac enlarge-

ment, heart failure, diastolic murmurs, or abnormal electrocardiograms, are a sign of organic heart disease. The over-all mortality for persons under 40 years of age with apical systolic murmurs is 3.25 times higher than the normally expected mortality rate and 4.5 times higher when there has been a history of rheumatic fever. The mortality rate is 50 per cent higher among manual workers with apical systolic murmur than among "white collar workers."

It should be evident then that the proper evaluation of the murmur is of paramount importance in medical practice both in war and in peace. Use of the term "loud apical systolic murmur" includes all grades of intensity except the extremely faint and slight and will include the moderately loud, loud, extremely loud, and unusually loud murmur (classification of Freeman and Levine). Physical examination, history, and laboratory examination are still of major importance in the final determination. A history of rheumatic fever in a patient with a loud murmur should be accepted as almost certain evidence that a defect in the mitral valve exists. The presence of a "musical, harsh, sea-gull, or constant murmur" strengthens the diagnosis. Patients should be examined repeatedly, in different positions and after exercise, since the murmurs of early valvular heart disease are transient.

Exercise will not produce "loud" apical murmurs in healthy persons. The teleroentgenogram and fluoroscope are of considerable import in diagnosis, as is the electrocardiogram. The occasional difficult differential diagnosis from the "effort syndrome" can usually be made on the basis of other well-recognized symptoms of neurocirculatory asthenia.

The author believes that loud systolic murmurs at the apex should therefore be considered organic, and the patient treated accordingly, receiving antibiotics during various manipulations and diseases which injure the mucous membranes and facilitate the entrance of bacteria into the blood stream which may lead to bacterial endocarditis. Establishment of the organic nature of a murmur does not afford a criterion of the heart's function.

BERNSTEIN.

**Tannenbaum, I., and Ferguson, J. A.: Rapid Deceleration and Rupture of the Aorta.** Arch. Path. **45**:503 (April), 1948.

This report deals with the possible importance of rapid deceleration as a factor in rupture of the aorta, a problem heretofore chiefly of interest in aviation medicine.

The authors record the presence of clean rupture of normal aortas following automobile accidents. In both instances the vehicle hit an immovable obstacle head-on. The drivers developed shock and died within a few minutes. Autopsy revealed aortic rupture at a classical site, namely, the junction of the descending aortic arch with the thoracic aorta.

The authors stress what they term "minimal damage to the thoracic cage," which is often in striking contrast to the rupture of a normal aorta.

GOULEY.

**Penneys, R., and Thomas, C. B.: Oximeter Control of Arterial Oxygen Saturation in Anoxemia Studies.** Bull. Johns Hopkins Hosp. **82**:470 (April), 1948.

The purpose of this study is to describe a procedure capable of producing the same constant level of anoxemia, which would remove an important obstacle in the standardization and further use of the "anoxemia test" of cardiac function. Its principle is based on the fact that by continuous fine adjustment of the oxygen concentration in a gas mixture, a constant degree of anoxemia, as measured by the oximeter, may be induced in the same and different individuals. This preliminary report is concerned with observations on normal subjects at levels of 85 per cent, 80 per cent, and 75 per cent arterial oxygen saturation. The lower level was set at 75 per cent for the following reasons: it is the approximate average arterial oxygen saturation resulting from 10 per cent oxygen inhalation; there is considerable cardiovascular stress at this point; and it provides a safe margin before marked central nervous system symptoms appear. The ability to produce and maintain any level of arterial oxygen saturation accurately depends more on the subject's being at ease than on any other factor.

The electrocardiograms were studied for any abnormalities, especially changes in the RS-T segments and T waves. In each of the four subjects studied at the three levels of anoxemia, 85 per cent, 80 per cent, and 75 per cent, no striking differences were observed between the various levels. Also, there were no marked differences noted between the electrocardiograms taken after ten and twenty minutes of anoxemia.

The oximeter was found to give the same degree of stability at the different levels. It can be said, therefore, that vasomotor changes due to anoxemia, and their effect on the thickness of the ear, do not alter the stability of the oximeter in the range of 75 to 100 per cent arterial saturation.

None of the subjects had symptoms at 85 per cent or 80 per cent arterial saturation. No changes in blood pressure, pulse, or respiration, necessitating termination of a test period, were encountered at these levels.

It is believed that this method is considerably more accurate than the currently used "induced anoxemia test" in which the subject inhales a gas with a fixed oxygen concentration (10 per cent).

BELLET.

**Lowe, T. E., and Bate, E. W.: The Diameter of Cardiac Muscle Fibres: A Study of the Diameter of Muscle Fibres in the Left Ventricle in Normal Hearts and in the Left Ventricular Enlargement of Simple Hypertension.** M. J. Australia 1:467 (April 10), 1948.

In this investigation the authors determined the transverse diameters of cardiac muscle fibers in each of the four major layers of the left ventricular wall in normal hearts and in hearts hypertrophied from simple hypertension. The hearts used in this investigation were five macroscopically normal ones from young adults and two from adults who had simple hypertension without congestive cardiac failure and who died noncardiac deaths. All hearts after fixation appeared to be in a comparable phase of partial systole.

In the normal hearts there was only a small variation in fiber size and the distribution of fibers of various sizes was symmetrical about the mean. There was also marked uniformity between the three outer layers, but the mean value for the inner layer was significantly smaller than that for the other layers. In the hypertrophied hearts there was enlargement of fibers and increase in the range of fiber size; the distribution of fiber size about the mean was symmetrical. In contrast to the finding in the normal hearts, the mean fiber size in the internal layer in this group was not significantly different from that in other layers.

Several methods of approach already considered suggest that there is a "limit of hypertrophy" of cardiac muscle fibers. This concept gives a ready explanation of the observation that the mean fiber size and distribution of fiber size in the two hypertrophied hearts examined were almost identical, despite the marked difference in weights. The marked difference in the weights of the hypertrophied hearts with the same fiber diameters shows that, in itself, heart weight is not necessarily a good index of the degree of muscle hypertrophy. The differences in weight must therefore be due to alterations in the amounts of interstitial fluid or tissue.

If the tension which a muscle fiber can develop is proportional to its cross-sectional area (Harrison), in each of the hearts examined a striking uniformity of tension in the muscle layers of the left ventricle can be deduced. In the hypertrophied hearts the mean cross-sectional area of fibers in each layer was the same. In the normal hearts, however, the mean cross-sectional areas of fibers, while uniform in the outer layers, were slightly but significantly less in the innermost layer. These observations imply, therefore, that in the normal heart the tensions are uniform in the outer three layers and slightly less in the innermost layers. In the hypertrophied hearts the tension seems to be uniform in all layers.

BELLET.

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## AMERICAN HEART ASSOCIATION AWARDS $250,000 FOR RESEARCH

The Board of Directors of the American Heart Association, on March 8, 1949, approved the report of the Research Committee and the Executive Committee of the Scientific Council allocating approximately $250,000 for fellowships for established investigators, research fellowships, and grants-in-aid.

The awards were made in accord with approved policies recommended by the Research Committee of the Scientific Council.

### *Research Policies*

The following policies, formulated by the Research Committee at its meeting in Chicago on February 26, 1949, were adopted as a guide in awarding research grants:

1. The funds allocated to individuals at present shall be given in major degree to Research Fellows as compared to Established Investigators.
2. Career Investigators shall not be appointed at the present time.
3. (a) Grants-in-Aid shall not be approved at the present time except in unusual circumstances.

(b) Fifteen per cent of the total research funds ($37,500) shall be granted for cooperative research studies (for example, The Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction).

4. Fluid Grants shall not be approved at the present time.
5. A decision concerning the division of funds for any particular cardiovascular disease or function is not warranted at the present time.
6. Ten per cent of the present funds allocated for research ($25,000) shall be given for basic research. Cooperation in this endeavor shall be sought with other large national voluntary organizations with the hope that a general Panel Committee of all of these may be formed to administer the funds contributed by them for basic research.
7. Funds shall not be approved for general teaching, nor for isolated statistical studies in clinical investigation.
8. Funds approved for Grants-in-Aid, or to individuals for Fellowships, shall be set aside for the current year only. Approval of a Grant-in-Aid or an Established Investigator shall include a statement of the duration of future support and a statement that such support will be contingent upon the availability of funds.

Applications for Fellowships shall be reviewed in October preceding the academic year in which the fellowship is desired, and research Grants-in-Aid for the individuals supported by these fellowships or other independent applications for Grants-in-Aid shall be considered in February preceding the academic year in which they are to start.

9. A separate contingency fund for research is not approved. However, the general reserve funds of the American Heart Association, after proper recommendation by the Research Committee, may be made available for the support of research in those unforeseeable circumstances which would call for immediate action.
10. It is anticipated that cooperative research will be participated in and supported by local heart associations and the American Heart Association will supplement these funds up to fifteen per cent of its present research funds.

## *Awards*

The following research awards were allocated for the period of one year to begin in most instances on July 1, 1949.* Indicated are the institutions or places where the research will be conducted.

I. *Established Investigators*

Awards totalling $12,500 were made to J. R. Elkinton, M.D. (University of Pennsylvania); W. Mommaerts, Ph.D. (Duke University).

II. *Research Fellowships*

Awards ranging from $3,000 to $4,000 each, and totalling $103,600, were allocated to the following: G. R. Denton (Albany Medical College); G. C. Sutton (Sweden); C. G. Sawyer (Peter Bent Brigham); T. G. Schnabel (University of Pennsylvania); P. Scheinberg (Duke University); E. Watkins, Jr. (University of Oregon); J. H. Heller (Yale University); R. J. Jones (University of Chicago); L. C. Mark (New York University); A. Genecin (Johns Hopkins University); E. Lepeschkin (University of Vermont); A. A. Brust (Cincinnati General Hospital); W. B. Schwartz (Harvard University); A. Mascatello (Long Island College of Medicine); L. S. Sommer (Columbia University); A. P. Fishman (Mt. Sinai Hospital, N. Y.); E. L. Foltz (University of Pennsylvania); W. W. Hurst (Deaconess Hospital, Great Falls, Mont.); C. A. Stetson (Rockefeller Institute, N. Y.); R. W. Oblath (May Institute, Los Angeles); F. J. Kelly (Tulane University); S. Kobernick (McGill University); L. Tobian, Jr. (Southwestern University); F. H. Taylor (Duke University); J. P. Merrill (Peter Bent Brigham); E. H. Kass (Good Samaritan Hospital, Boston, Mass.); J. E. Warren (Good Samaritan Hospital, Boston, Mass.); R. E. Olson (Harvard University); A. G. White (Montefiore Hospital, N. Y.).

III. *Research Grants-In-Aid*

Research grants totalling $23,730 were made to the following investigators: R. F. Loeb (Columbia University); R. M. Reinecke (University of Minnesota); C. H. Thienes (University of Southern California); D. A. Rytand (Stanford University); O. W. Sartorius (Syracuse University); R. E. Gross (Children's Hospital, Boston).

Grants of $11,235 to the following were approved and will be allocated if funds are available: Mary Colglazier (University of Kansas); E. Watkins, Jr. (University of Oregon); J. R. DiPalma (Long Island College of Medicine); J. J. Sampson (Mt. Zion Hospital, San Francisco).

## *Grant-In-Aid for Training Program*

Allocation of $16,170 was approved for the establishment of a special training program for cardiovascular investigators under Dr. Carl J. Wiggers at Western Reserve University. The program will be supported on a cooperative basis with the National Heart Institute. Under this plan, a maximum of ten investigators selected by Dr. Wiggers will receive training in various research methods employed in human and in animal cardiovascular research for a period of one year. The National Heart Institute will support the individuals chosen for this program, and the American Heart Association is supporting the cost of the training program.

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*$25,000 was awarded to Dr. Albert St. Gyorgyi for research on muscular contraction by the Board of Directors last June.

### *Research Fellow of the Cardiovascular Registry*

A resolution was approved by the Board of Directors providing for the establishment of a Research Fellowship for the Cardiovascular Registry of the American Registry of Pathology from the funds allocated for cooperative research studies. The funds will be administered by the Advisory Committee on Cardiovascular Registry.

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Further information about these grants and present policies of the Research Committee may be obtained by writing to Dr. Charles A. R. Connor, Medical Director, American Heart Association.

### ANNOUNCEMENT

A symposium on Water and Electrolyte Metabolism in Cardiac Edema, sponsored by the Cardiovascular Study Section of the National Institutes of Health of the Public Health Service, will be held on April 30, 1949, at Hotel Haddon Hall, Atlantic City. Dr. E. Cowles Andrus, Baltimore, is Chairman of the Cardiovascular Study Section.

It will be appreciated if those who expect to attend will communicate with Dr. Eleanor M. K. Darby, National Institutes of Health, Bethesda, Maryland, Executive Secretary.

### THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

The American Society for the Study of Arteriosclerosis will meet in Chicago, November 6-7, 1949. Titles submitted for the program must be in the hands of the Chairman of the Program Committee, E. Cowles Andrus, M.D., 24 East Eager Street, Baltimore 2, Md., by June 15. Titles should be accompanied by an abstract of not more than 300 words.